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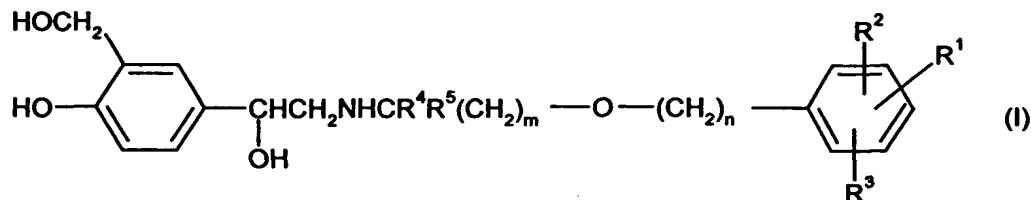
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(54) Title: AGONISTS OF BETA-ADRENOCEPTORS

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(57) Abstract: The present invention relates to novel compounds of formula (I), to a process for their manufacture, to pharmaceutical compositions containing them, and to their use in therapy, in particular their use in the prophylaxis and treatment of respiratory diseases.

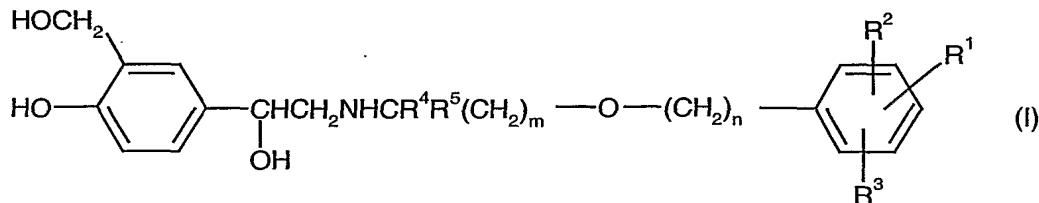
AGONISTS OF BETA-ADRENOCEPTORS

The present invention is concerned with phenethanolamine derivatives, processes for their preparation, compositions containing them and their use in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

Certain phenethanolamine compounds are known in the art as having selective stimulant action at β_2 -adrenoreceptors and therefore having utility in the treatment of bronchial asthma and related disorders. Thus GB 2 140 800 describes phenethanolamine compounds including 4-hydroxy- α^1 -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of such medical conditions.

Although salmeterol and the other commercially available β_2 -adrenoreceptor agonists are effective bronchodilators, the maximum duration of action is 12 hours, hence twice daily dosing is often required. There is therefore a clinical need for compounds having potent and selective stimulant action at β_2 -adrenoreceptors and having an advantageous profile of action.

According to the present invention, there is provided a compound of formula (I)



or a salt, solvate, or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8;

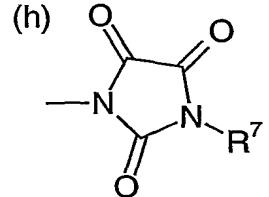
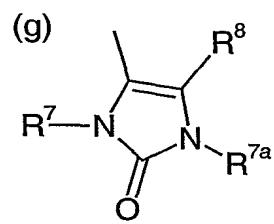
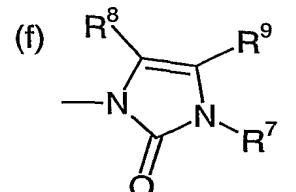
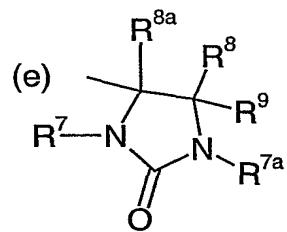
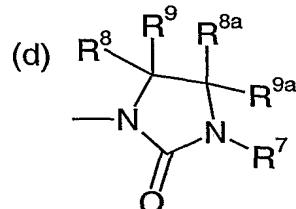
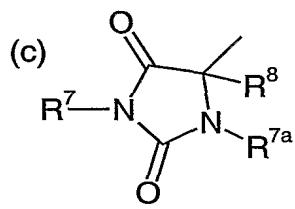
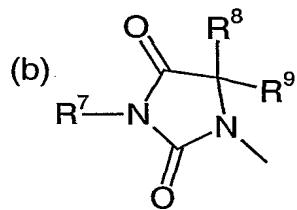
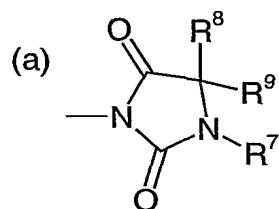
n is an integer of from 3 to 11, preferably from 3 to 7;

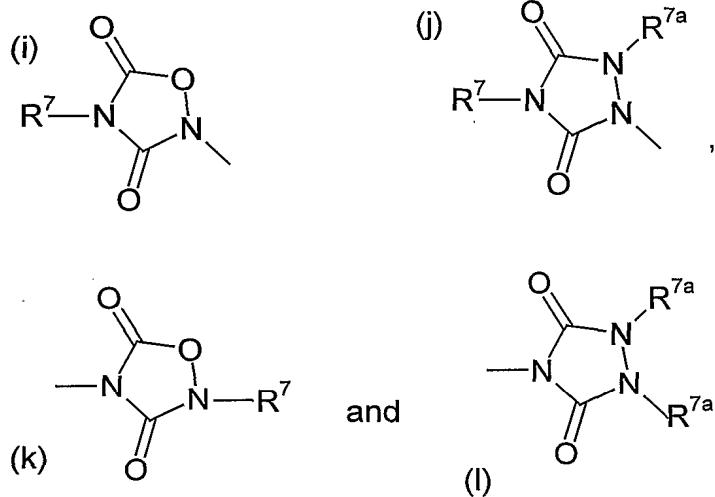
with the proviso that m + n is 5 to 19, preferably 5 to 12;

R^1 is $-X-R^6$; wherein

X is selected from $-(CH_2)_p-$ and C_{2-6} alkenylene;

5 R^6 is selected from





5 R⁷ and R^{7a} are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, C(O)R^{7b}, C(O)NHR^{7b}, phenyl, naphthyl, hetaryl, and phenyl(C₁₋₄alkyl)-, and R⁷ and R^{7a} are optionally substituted by 1 or 2 groups independently selected from halo, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, -NHC(O)(C₁₋₆alkyl), -SO₂(C₁₋₆alkyl), -SO₂(phenyl), -CO₂H, and -CO₂(C₁₋₄alkyl);

10

R^{7b} is selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, phenyl, naphthyl, hetaryl, and phenyl(C₁₋₄alkyl), and R^{7b} is optionally substituted by 1 or 2 groups independently selected from halo, C₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆haloalkyl, -NHC(O)(C₁₋₆alkyl), -SO₂(C₁₋₆alkyl), -SO₂(phenyl), -CO₂H, and -CO₂(C₁₋₄alkyl);

15

R⁸, R^{8a}, R⁹ and R^{9a} are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₇cycloalkyl, phenyl, naphthyl, hetaryl, phenyl(C₁₋₄alkyl)-, -NR^{10a}SO₂R¹⁰, -NR^{10a}C(O)NR¹⁰R¹¹, -SO₂NR¹⁰R¹¹, and C₁₋₆alkyl substituted by -CO₂R¹⁰ or -C(O)NR¹⁰R¹¹;

20

R¹⁰, R^{10a} and R¹¹ are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and phenyl (C₁₋₄alkyl)-;

p is an integer from 0 to 6, preferably from 0 to 4:

R² is selected from hydrogen, C₁₋₆alkyl, C₁₋₆alkoxy, phenyl, halo, and C₁₋₆haloalkyl;

5 R³ is selected from hydrogen, hydroxyl, C₁₋₆alkyl, C₁₋₆alkoxy, phenyl, halo, C₁₋₆haloalkyl, -NR⁷CONR^{7a} and -SO₂NR^aR^b;

10 wherein R^a and R^b are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and phenyl (C₁₋₄alkyl), or R^a and R^b, together with the

nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring;

and R^a and R^b are each optionally substituted by one or two groups selected from halo, C₁₋₆alkyl, and C₁₋₆haloalkyl; and

15 R⁴ and R⁵ are independently selected from hydrogen and C₁₋₄alkyl with the proviso that the total number of carbon atoms in R⁴ and R⁵ is not more than 4.

In the definition of X, the term alkenylene includes both *cis* and *trans* structures.

Examples of suitable alkenylene groups include -CH=CH-.

20 In the definition of R³, where R^a and R^b together with the nitrogen atom to which they are bonded form a 5-, 6- or 7- membered nitrogen containing ring the term "5-, 6-, or 7-membered nitrogen containing ring" means a 5-, 6-, or 7- membered saturated or unsaturated ring which includes the sulphonamide nitrogen atom and optionally 1 or 2 other heteroatoms independently selected from nitrogen, sulphur, and oxygen. Suitable examples of such a ring include piperidinyl, morpholinyl, and piperazinyl.

25 In the definition of R⁷, the term "hetaryl" means a 5- or 6-membered heteroaromatic ring, such as thienyl, pyridyl or imidazolyl.

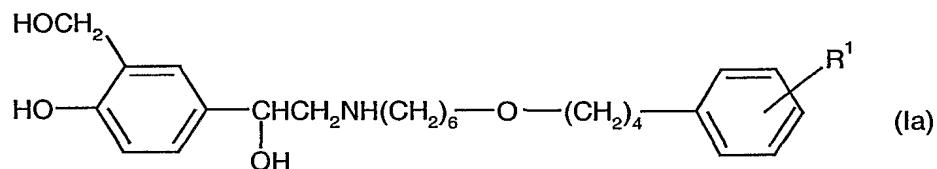
30 In the compounds of formula (I) R² and R³ preferably each represent hydrogen.

In the compounds of formula (I), R⁴ and R⁵ are preferably independently selected from hydrogen and methyl, more preferably R⁴ and R⁵ are both hydrogen.

In the compounds of formula (I), m is suitably 3, 4, 5 or 6 and n is suitably 3, 4, 5 or 6.

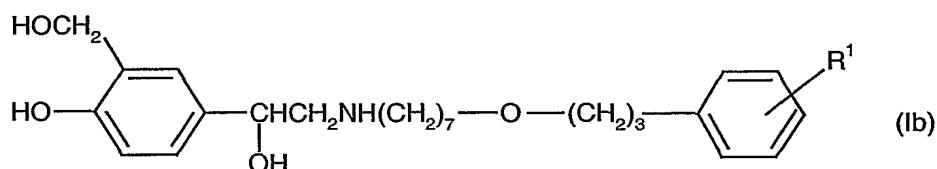
5 Preferably m is 5 and preferably n is 4 or 5, such that m + n is 8, 9 or 10, preferably 9.

According to a preferred aspect of the invention, there is provided a compound of formula (Ia)



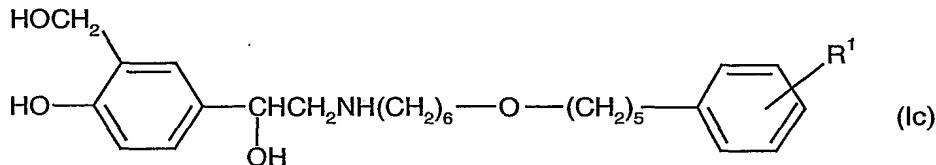
or a salt, solvate, or physiologically functional derivative thereof, wherein R¹ is as defined above for formula (I).

15 According to a further preferred aspect of the invention, there is provided a compound of formula (Ib)



20 or a salt, solvate, or physiologically functional derivative thereof, wherein R¹ is as defined above for formula (I).

According to a yet further preferred aspect of the invention, there is provided a compound of formula (Ic):



or a salt, solvate, or physiologically functional derivative thereof, wherein R^1 is a defined
5 above for formula (I).

Compounds or formulae (Ia) and (Ic) are particularly preferred.

In the compounds of formulae (I), (Ia), (Ib) and (Ic) the group R^1 is preferably attached
10 to the meta-position relative to the $-\text{O}-(\text{CH}_2)_n-$, $-\text{O}-(\text{CH}_2)_4-$, $-\text{O}-(\text{CH}_2)_3-$ or $-\text{O}-(\text{CH}_2)_5$ link
respectively.

In the compounds of formulae (I), (Ia), (Ib) and (Ic) the group R^6 is preferably linked to
15 the moiety X or directly to the phenyl ring via one of the ring nitrogen atoms of the group
 R^6 . Advantageously the group R^6 is selected from the groups (a), (b), (d) and (f).

In the compounds of formulae (I), (Ia), (Ib) and (Ic), R^7 , R^{7a} , R^8 , R^{8a} , R^9 and R^{9a} are
preferably all hydrogen.

20 Particularly preferred are compounds wherein R^6 is selected from the groups (a), (b), (d)
and (f) and R^7 , R^{7a} , R^8 and R^9 are all hydrogen.

Also particularly preferred are compounds wherein R^6 is a group (a) and R^8 represents $-\text{NHCONH}_2$ and compounds wherein R^6 is a group (b) and R^7 represents $-\text{CH}_2\text{CONH}_2$.

25 It is to be understood that the present invention covers all combinations of particular and
preferred groups described hereinabove.

The compounds of formulae (I), (Ia), (Ib) and (Ic) include an asymmetric centre, namely the carbon atom of the



- 5 group. The present invention includes both (S) and (R) enantiomers either in substantially pure form or admixed in any proportions. Preferably, the compounds of the invention are in the form of the (R) enantiomers.

10 Similarly, where R⁴ and R⁵ are different groups, the carbon atom to which they are attached is an asymmetric centre and the present invention includes both (S) and (R) enantiomers at this centre either in substantially pure form or admixed in any proportions.

15 Thus the compounds of formulae (I), (Ia), (Ib) and (Ic) include all enantiomers and diastereoisomers as well as mixtures thereof in any proportions.

Preferred compounds of the invention include:

- 20 3-[3-(4-{[6-({2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}-amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione;
- 3-[3-(3-{[7-({2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}-amino)heptyl]oxy}propyl)phenyl]imidazolidine-2,4-dione;
- 1-[3-(4-{[6-({2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]imidazolidin-2-one;
- 25 1-[3-(4-{[6-({2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}-amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione;
- 3-[3-(4-{[6-([(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione;
- 3-[3-(4-{[6-([(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione;
- 30 3-[3-(4-{[6-([(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione;
- 3-[3-(4-{[6-([(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione;

- 3-[3-(4-{{(2S)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione;
3-[4-(4-{{[6-({{(2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione;
5 3-[2-(4-{{[6-({{(2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione;
3-[3-(4-{{[6-({{(2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl)benzyl]imidazolidine-2,4-dione;
3-[3-(5-{{[5-({{(2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino}pentyl]oxy}pentyl)phenyl]imidazolidine-2,4-dione;
10 3-[3-(5-{{[6-({{(2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}pentyl)phenyl]imidazolidine-2,4-dione;
3-[3-(6-{{[6-({{(2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}hexyl)phenyl]imidazolidine-2,4-dione;
15 15 (5R)-5-[3-(4-{{[6-({{(2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl)benzyl]-5-methylimidazolidine-2,4-
dione;
(5S)-5-[3-(4-{{[6-({{(2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl)benzyl]-5-methylimidazolidine-2,4-
20 dione;
2-{3-[3-(4-{{[6-({{(2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl)phenyl]-2,4-dioxoimidazolin-1-
yl}acetamide;
5-[4-(4-{{[6-({{(2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl)benzyl]imidazolidine-2,4-dione;
25 1-[3-(4-{{[6-({{(2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl)phenyl]-1,3-dihydro-2*H*-imidazol-2-
one;
3-[3-(4-{{[6-({{(2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl)phenyl]-5,5-dimethylimidazolidine-
30 2,4-dione;

- 3-[3-(3-{{(2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)heptyl]oxy]propyl)phenyl]-1-
(methylsulfonyl)imidazolidine-2,4-dione;
1-[3-(3-{{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}propyl)phenyl]imidazolidine-2,4-dione;
5 N-{1-[3-(4-{{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)benzyl]-2,5-dioxoimidazolidin-4-
yl}urea;
3-benzyl-1-[3-(4-{{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione;
10 1-[3-(4-{{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]-3-methylimidazolidine-2,4-
dione;
{3-[3-(4-{{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]-2,5-dioxoimidazolidin-1-yl};
15 2-{3-[3-(4-{{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]-2,5-dioxoimidazolidin-1-
yl}acetamide;
1-[3-(4-{{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)benzyl]imidazolidine-2,4-dione;
20 1-Benzyl-3-[3-(4-{{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione;
3-[3-(4-{{[6-((2R)-2-Hydroxy-2-[4-hydroxy-3-
25 (hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]-1-
(methylsulfonyl)imidazolidine-2,4-dione; and
4-[3-(4-{{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]-1,2,4-triazolidine-3,5-dione;
30 and salts, solvates, and physiologically functional derivatives thereof.

Particularly preferred compounds of the invention include:

10

- 3-[3-(4-{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]-amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione;
3-[3-(4-{[6-((2S)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]-amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione;
5 3-[3-(4-{[6-((2R/S)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]-amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione;
2-{3-[3-(4-{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy}butyl)phenyl]-2,5-dioxoimidazolidin-1-yl}acetamide acetate;
10 N-[1-[3-(4-{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy}butyl)benzyl]-2,5-dioxoimidazolidin-4-yl]urea acetate;
3-[3-(5-{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy}pentyl)phenyl]imidazolidine-2,4-dione
15 acetate;

and salts, solvates, and physiologically functional derivatives thereof.

Especially preferred is 3-[3-(4-{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]-amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione and salts, solvates, and physiologically functional derivatives thereof.

Salts and solvates of compounds of formulae (I), (Ia), (Ib) and (Ic) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formulae (I), (Ia), (Ib) and (Ic) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives.

By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I), (Ia), (Ib) or (Ic) having the same physiological function as the free compound of formula (I), (Ia) (Ib) and (Ic), for example, by being convertible in the

body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

Suitable salts according to the invention include those formed with both organic and
5 inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulphonic (for example p-toluenesulphonic, benzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic, tricarballylic, cinnamic, substituted cinnamic (for example, phenyl, methyl, methoxy or halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacrylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

20
Pharmaceutically acceptable esters of the compounds of formula (I), (Ia), (Ib) and (Ic) may have a hydroxyl group converted to a C₁₋₆alkyl, aryl, aryl C₁₋₆ alkyl, or amino acid ester.

25 As mentioned above, the compounds of formulae (I), (Ia), (Ib) and (Ic) are selective β₂-adrenoreceptor agonists as demonstrated using functional or reporter gene readout from cell lines transfected with human beta-adrenoreceptors as described below. Compounds according to the present invention also have the potential to combine long duration of effect with rapid onset of action. Furthermore, certain compounds have
30 shown an improved therapeutic index in animal models relative to existing long-acting β₂-agonist bronchodilators. As such, compounds of the invention may be suitable for once-daily administration.

12

Therefore, compounds of formulae (I), (Ia), (Ib) and (Ic) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2 -adrenoreceptor agonist is indicated. Such conditions include diseases associated with reversible

5 airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

Other conditions which may be treated include premature labour, depression, 10 congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

Accordingly, the present invention provides a method for the prophylaxis or treatment of

15 a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I), (Ia), (Ib) and (Ic), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. In particular,

the present invention provides such a method for the prophylaxis or treatment of a

20 disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect the present invention provides such a method for the

prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable

25 (e.g. peptic and gastric ulceration) or muscle wasting disease.

In the alternative, there is also provided a compound of formula (I), (Ia), (Ib) or (Ic) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof

30 for use in medical therapy, particularly, for use in the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2 -adrenoreceptor agonist is indicated. In particular, there is provided a compound of

formula (I), (Ia), (Ib) or (Ic) or a pharmaceutically acceptable salt, solvate, or

physiologically functional derivative thereof for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

In a further aspect, there is provided a compound of formula (I), (Ia), (Ib) or (Ic) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

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The present invention also provides the use of a compound of formula (I), (Ia), (Ib) or (Ic) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2 -adrenoreceptor agonist is indicated, for example a disease associated with reversible airways obstruction such as asthma,

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chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I), (Ia), (Ib) or (Ic), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or

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treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

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The amount of a compound of formula (I), (Ia), (Ib) or (Ic), or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The compounds of the invention may be administered by

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inhalation at a dose of from 0.0005mg to 10 mg, preferably 0.005mg to 0.5mg. The dose range for adult humans is generally from 0.0005 mg to 100mg per day and preferably 0.01 mg to 1mg per day.

While it is possible for the compound of formula (I), (Ia), (Ib) or (Ic), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to be administered alone, it is preferable to present it as a pharmaceutical formulation.

- 5 Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I), (Ia), (Ib) or (Ic) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.
- 10 Hereinafter, the term "active ingredient" means a compound of formula (I), (Ia), (Ib) or (Ic), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

15 The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The 20 formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely 25 divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

30 Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

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Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

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Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier substance) such as lactose or starch. Use of lactose is preferred. Each capsule or cartridge may generally contain between 20 μ g-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients. Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device

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is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a

5 compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole
10 width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from

15 pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly
20 hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid
25 or lecithin and cosolvents eg ethanol. Pressurised formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size.

30 The optimum particle size for inhalation into the bronchial system is usually 1-10 μm , preferably 2-5 μm . Particles having a size above 20 μm are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means eg by

micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90 μ m and not less than 15% will have a MMD of less than 15 μ m.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Solutions for inhalation by nebulisation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example selected from anti-inflammatory agents, anticholinergic agents (particularly an M₁, M₂, M₁/M₂ or M₃ receptor antagonist), other β₂-adrenoreceptor agonists, antiinfective agents
5 (e.g. antibiotics, antivirals), or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with one or more other therapeutically active agents, for example selected from an anti-inflammatory agent (for example a corticosteroid or an NSAID), an anticholinergic
10 agent, another β₂-adrenoreceptor agonist, an antiinfective agent (e.g. an antibiotic or an antiviral), or an antihistamine. Preferred are combinations comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid, and/or an anticholinergic, and/or a PDE-4 inhibitor. Preferred combinations are those comprising one or two other
15 therapeutic agents.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. hydrates) to optimise the activity and/or stability and/or physical characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate, the therapeutic ingredients may be used in optically pure form.

Suitable anti-inflammatory agents include corticosteroids and NSAIDs. Suitable
25 corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid S-fluoromethyl
30 ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy- androsta-1,4-diene-17β-carbothioic acid S-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide,

rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, $6\alpha,9\alpha$ -difluoro- 11β -hydroxy- 16α -methyl- 17α -[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene- 17β -carbothioic acid *S*-fluoromethyl ester and $6\alpha,9\alpha$ -difluoro- 17α -[(2-furanylcarbonyl)oxy]- 11β -hydroxy- 16α -methyl-3-oxo-androsta-1,4-diene- 17β -carbothioic acid *S*-fluoromethyl ester, more preferably $6\alpha,9\alpha$ -difluoro- 17α -[(2-furanylcarbonyl)oxy]- 11β -hydroxy- 16α -methyl-3-oxo-androsta-1,4-diene- 17β -carbothioic acid *S*-fluoromethyl ester.

Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase

(PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis. Suitable other β_2 -adrenoreceptor agonists include salmeterol (e.g. as the xinafoate), salbutamol (e.g. as the sulphate or the free base), formoterol (e.g. as the fumarate), fenoterol or terbutaline and salts thereof.

Of particular interest is use of the compound of formula (I) in combination with a

phosphodiesterase 4 (PDE4) inhibitor or a mixed PDE3/PDE4 inhibitor. The PDE4-specific inhibitor useful in this aspect of the invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 inhibitor which has an IC₅₀ ratio of about 0.1 or greater as regards the IC₅₀ for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC₅₀ for the form which binds rolipram with a low affinity. For the purposes of this disclosure, the cAMP catalytic site which binds R and S rolipram with a low affinity is denominated the "low affinity" binding site (LPDE 4) and the other form of this catalytic site which binds rolipram with a high affinity is denominated the "high affinity" binding site (HPDE 4). This term "HPDE4" should not be confused with the term "hPDE4" which is used to denote human PDE4.

Initial experiments may be conducted to establish and validate a [³H]-rolipram binding assay. Details of this work are given in the Binding Assays described in detail below.

Phosphodiesterase and Rolipram Binding Assays

5 Assay method 1A

Isolated human monocyte PDE4 and hrPDE (human recombinant PDE4) was determined to exist primarily in the low affinity form. Hence, the activity of test compounds against the low affinity form of PDE4 can be assessed using standard assays for PDE4 catalytic activity employing 1 μ M [³H]cAMP as a substrate (Torphy *et al.*, J. of Biol. Chem., Vol. 267, No. 3 pp1798-1804, 1992).

Rat brain high speed supernatants were used as a source of protein and both enantiomers of [³H]-rolipram were prepared to a specific activity of 25.6 Ci/mmol. Standard assay conditions were modified from the published procedure to be identical to the PDE assay conditions, except for the last of the cAMP: 50mM Tris HCl (pH 7.5), 15 5 mM MgCl₂, 50 μ M 5'-AMP and 1 nM of [³H]-rolipram (Torphy *et al.*, J. of Biol. Chem., Vol. 267, No. 3 pp1798-1804, 1992). The assay was run for 1 hour at 30° C. The reaction was terminated and bound ligand was separated from free ligand using a Brandel cell harvester. Competition for the high affinity binding site was assessed under conditions that were identical to those used for measuring low affinity PDE 20 activity, expect that [³H]-cAMP was not present.

Assay method 1B

Measurement of Phosphodiesterase Activity

PDE activity was assayed using a [³H]cAMP SPA or [³H]cGMP SPA enzyme assay as 25 described by the supplier (Amersham Life Sciences). The reactions were conducted in 96-well plates at room temperature, in 0.1 ml of reaction buffer containing (final concentrations): 50 mM Tris-HCl, pH 7.5, 8.3 mM MgCl₂, 1.7 mM EGTA, [³H]cAMP or [³H] cGMP (approximately 2000 dpm/pmol), enzyme and various concentrations of the inhibitors. The assay was allowed to proceed for 1 hr and was terminated by adding 50 30 μ l of SPA yttrium silicate beads in the presence of zinc sulfate. The plates were shaken and allowed to stand at room temperature for 20 min. Radiolabeled product formation was assessed by scintillation spectrometry.

[³H]R-rolipram binding assay

The [³H]R-rolipram binding assay was performed by modification of the method of Schneider and co-workers, see Nicholson, et al., Trends Pharmacol. Sci., Vol. 12, pp.19-27 (1991) and McHale et al., Mol. Pharmacol., Vol. 39, 109-113 (1991). R-

- 5 Rolipram binds to the catalytic site of PDE4 see Torphy et al., Mol. Pharmacol., Vol. 39, pp. 376-384 (1991). Consequently, competition for [³H]R-rolipram binding provides an independent confirmation of the PDE4 inhibitor potencies of unlabeled competitors. The assay was performed at 30°C for 1 hr in 0.5 µl buffer containing (final concentrations): 50 mM Tris-HCl, pH 7.5, 5 mM MgCl₂, 0.05% bovine serum albumin, 2 nM [³H]R-rolipram (5.7 x 104 dpm/pmol) and various concentrations of non-radiolabeled inhibitors.
- 10 The reaction was stopped by the addition of 2.5 ml of ice-cold reaction buffer (without [³H]-R-rolipram) and rapid vacuum filtration (Brandel Cell Harvester) through Whatman GF/B filters that had been soaked in 0.3% polyethylenimine. The filters were washed with an additional 7.5 ml of cold buffer, dried, and counted via liquid scintillation spectrometry.
- 15

- 20 The preferred PDE4 inhibitors of use in this invention will be those compounds which have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP catalytic activity where the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects which apparently are linked to inhibiting the form which binds rolipram with a high affinity. Another way to state this is that the preferred compounds will have an IC₅₀ ratio of about 0.1 or greater as regards the IC₅₀ for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC₅₀ for the form which binds rolipram with a low affinity.

- 25 A further refinement of this standard is that of one wherein the PDE4 inhibitor has an IC₅₀ ratio of about 0.1 or greater; said ratio is the ratio of the IC₅₀ value for competing with the binding of 1nM of [³H]R-rolipram to a form of PDE4 which binds rolipram with a high affinity over the IC₅₀ value for inhibiting the PDE4 catalytic activity of a form which binds rolipram with a low affinity using 1 µM[³H]-cAMP as the substrate.
- 30

Examples of useful PDE4 inhibitors are:

(R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone;

(R)-(+)-1-(4-bromobenzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone;
3-(cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N2-cyano-S-methyl-isothioureido]benzyl)-
2-pyrrolidone;
cis 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid];
5 cis-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol];
(R)-(+)-ethyl [4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidine-2-ylidene]acetate; and
(S)-(--)ethyl [4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidine-2-ylidene]acetate.

Most preferred are those PDE4 inhibitors which have an IC₅₀ ratio of greater than 0.5,

10 and particularly those compounds having a ratio of greater than 1.0. Preferred
compounds are *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-
carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-
difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-
difluoromethoxyphenyl)cyclohexan-1-ol]; these are examples of compounds which bind
15 preferentially to the low affinity binding site and which have an IC₅₀ ratio of 0.1 or
greater.

Other compounds of interest include:

20 Compounds set out in U.S. patent 5,552,438 issued 03 September, 1996; this patent
and the compounds it discloses are incorporated herein in full by reference. The
compound of particular interest, which is disclosed in U.S. patent 5,552,438, is *cis*-4-
cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also
known as cilomalast) and its salts, esters, pro-drugs or physical forms;

25 AWD-12-281 from Asta Medica (Hofgen, N. et al. 15th EFMC Int Symp Med Chem
(Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-
benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience
and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-
168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko
30 in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. et al.
Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl.
28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone
(WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-

Gulden; Pumafentrine, (-)-p-[(4aR*,10bS*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from 5 Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. *et al.* J Pharmacol Exp Ther, 1998, 284(1): 162), and T2585.

Other possible PDE-4 and mixed PDE3/PDE4 inhibitors include those listed in WO01/13953, the disclosure of which is hereby incorporated by reference.

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Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M₁ and M₂ receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these 15 compounds are normally administered as a salt, being tertiary amines. These drugs, particularly the salt forms, are readily available from a number of commercial sources or can be made or prepared from literature data via, to wit:

Atropine - CAS-51-55-8 or CAS-51-48-1 (anhydrous form), atropine sulfate - CAS-5908-99-6; atropine oxide - CAS-4438-22-6 or its HCl salt - CAS-4574-60-1 and

20 methylatropine nitrate - CAS-52-88-0.

Homatropine - CAS-87-00-3, hydrobromide salt - CAS-51-56-9, methylbromide salt - CAS-80-49-9.

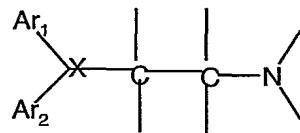
Hyoscyamine (*d, l*) - CAS-101-31-5, hydrobromide salt - CAS-306-03-6 and sulfate salt - CAS-6835-16-1.

25 Scopolamine - CAS-51-34-3, hydrobromide salt - CAS-6533-68-2, methylbromide salt - CAS-155-41-9.

Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) 30 (CAS-139404-48-1). Also of interest are: methantheline (CAS-53-46-3), propantheline bromide (CAS- 50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- 80-50-2), clidinium bromide (Quarzan, CAS-3485-62-9), copyrrolate (Robinul), isopropamide iodide (CAS-71-81-8), mepenzolate bromide (U.S. patent 2,918,408), tridihexethyl

chloride (Pathilone, CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also cyclopentolate hydrochloride (CAS-5870-29-1), tropicamide (CAS-1508-75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29868-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methocetramine, and the
 5 compounds disclosed in WO01/04118, the disclosure of which is hereby incorporated by reference.

Suitable antihistamines (also referred to as H₁-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H₁-receptors, and are safe for
 10 human use. All are reversible, competitive inhibitors of the interaction of histamine with H₁-receptors. The majority of these inhibitors, mostly first generation antagonists, have a core structure, which can be represented by the following formula:



15 This generalized structure represents three types of antihistamines generally available: ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperazine and phenothiazines. Second generation antagonists, which are non-sedating, have a
 20 similar structure-activity relationship in that they retain the core ethylene group (the alkylamines) or mimic the tertiary amine group with piperazine or piperidine. Exemplary antagonists are as follows:

Ethanolamines: carboxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate.
 25 Ethylenediamines: pyrilamine amleate, tripelennamine HCl, and tripelennamine citrate.
 Alkylamines: chlorpheniramine and its salts such as the maleate salt, and acrivastine.
 Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.
 30 Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H₁ receptor antagonist which may be used in combination with a PDE4 inhibitor.

Examples of preferred anti-histamines include methapyrilene and loratadine.

- 5 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor.
- 10 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid.
- 15 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic.
- 20 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an antihistamine.
- 25 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor and a corticosteroid.
- 30 The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic and a PDE-4 inhibitor.
- The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a physiologically acceptable diluent or carrier represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

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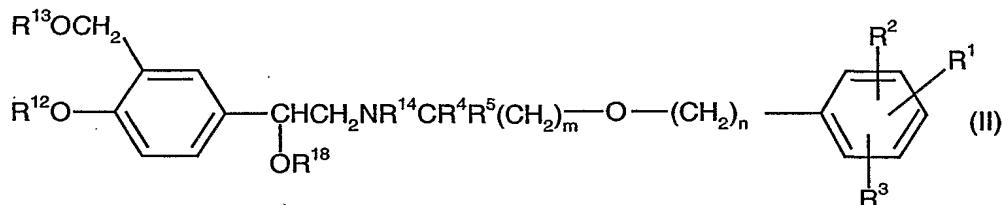
According to a further aspect of the invention, there is provided a process for preparing a compound of formula (I), (Ia), (Ib) or (Ic) or a salt, solvate, or physiologically functional derivative thereof which comprises a process (a), (b), (c), (d) or (e) as defined below followed by the following steps in any order:

10

- (i) optional removal of any protecting groups;
- (ii) optional separation of an enantiomer from a mixture of enantiomers;
- (iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

15

In one general process (a), a compound of formula (I), (Ia), (Ib) or (Ic) may be obtained by deprotection of a protected intermediate, for example of formula (II):



or a salt or solvate thereof, wherein R¹, R², R³, R⁴, R⁵, m, and n are as defined for the compound of formula (I), (Ia), (Ib) or (Ic), and R¹², R¹³, and R¹⁴ are each independently either hydrogen or a protecting group provided that at least one of R¹², R¹³, and R¹⁴ is a protecting group, and R¹⁸ is either hydrogen or a protecting group.

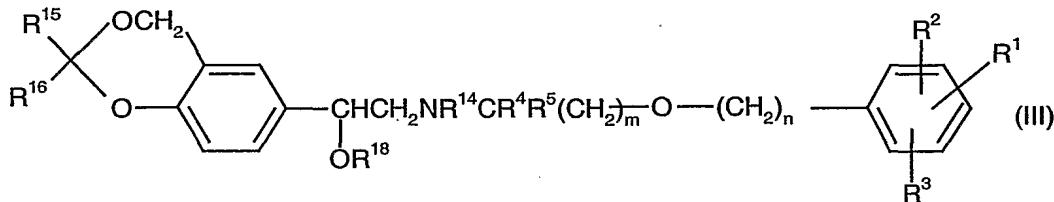
Suitable protecting groups may be any conventional protecting group such as those described in "Protective Groups in Organic Synthesis" by Theodora W Greene and Peter G M Wuts, 3rd edition (John Wiley & Sons, 1999). Examples of suitable hydroxyl protecting groups represented by R¹² and R¹³ are esters such as acetate ester, aralkyl groups such as benzyl, diphenylmethyl, or triphenylmethyl, and tetrahydropyranyl.

Examples of suitable amino protecting groups represented by R¹⁴ include benzyl, α-methylbenzyl, diphenylmethyl, triphenylmethyl, benzyloxycarbonyl, tert-butoxycarbonyl, and acyl groups such as trichloroacetyl or trifluoroacetyl.

- 5 As will be appreciated by the person skilled in the art, use of such protecting groups may include orthogonal protection of groups in the compounds of formula (II) to facilitate the selective removal of one group in the presence of another, thus enabling selective functionalisation of a single amino or hydroxyl function. For example, the –CH(OH) group may be orthogonally protected as –CH(OR¹⁸) using, for example, a trialkylsilyl group such as triethylsilyl. A person skilled in the art will also appreciate other orthogonal protection strategies, available by conventional means as described in
- 10 Theodora W Greene and Peter G M Wuts (see above).

- 15 The deprotection to yield a compound of formula (I), (Ia), (Ib) or (Ic) may be effected using conventional techniques. Thus, for example, when R¹², R¹³, and/or R¹⁴ is an aralkyl group, this may be cleaved by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal).

- 20 When R¹² and/or R¹³ is tetrahydropyanyl this may be cleaved by hydrolysis under acidic conditions. Acyl groups represented by R¹⁴ may be removed by hydrolysis, for example with a base such as sodium hydroxide, or a group such as trichloroethoxycarbonyl may be removed by reduction with, for example, zinc and acetic acid. Other deprotection methods may be found in Theodora W Greene and Peter G M Wuts (see above). In a particular embodiment of process (a), R¹² and R¹³ may together represent a protecting group as in the compound of formula (III):
- 25

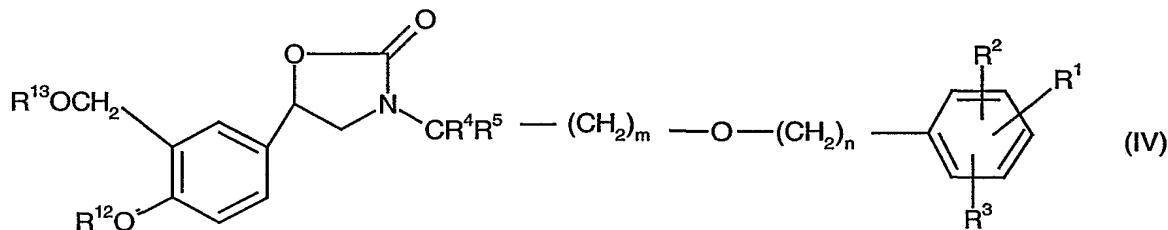


or a salt or solvate thereof, wherein R¹, R², R³, R⁴, R⁵, R¹⁴, R¹⁸ m, and n are as defined for the compound of formula (I), (Ia), (Ib) or (Ic), R¹⁵ and R¹⁶ are independently selected from hydrogen, C₁₋₆alkyl, or aryl. In a preferred aspect, both R¹⁵ and R¹⁶ are methyl.

- 5 The compound of formula (III) may be converted to a compound of formula (I), (Ia), (Ib) or (Ic) by hydrolysis with dilute aqueous acid, for example acetic acid or hydrochloric acid in a suitable solvent or by transketalisation in an alcohol, for example ethanol, in the presence of a catalyst such as an acid (for example, toluenesulphonic acid) or a salt (such as pyridinium tosylate) at normal or elevated temperature.

- 10 It will be appreciated that the protecting groups R¹², R¹³, R¹⁴ and R¹⁸ (including the cyclised protecting group formed by R¹⁵ and R¹⁶ as depicted in formula (III)) may be removed in a single step or sequentially. The precise order in which protecting groups are removed will in part depend upon the nature of said groups and will be readily apparent to the skilled worker. Preferably, when R¹⁵ and R¹⁶ together form a protecting group as in formula (III) this protecting group is removed together with any protecting group on the CH(OH) moiety, followed by removal of R¹⁴.

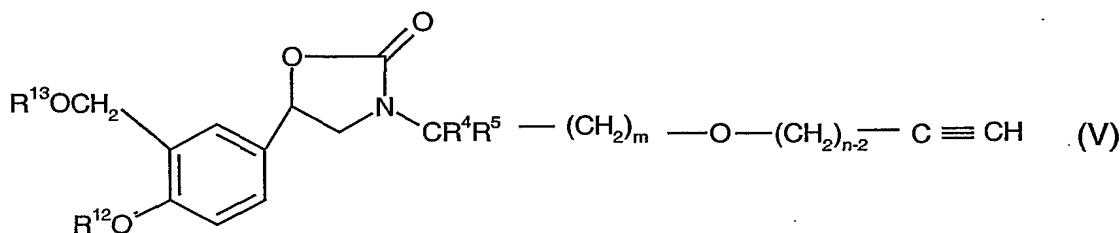
- 15 Depending on the nature of the group R⁶, some compounds of formulae (II) and (III) wherein R¹⁴ is hydrogen may be prepared from the corresponding compound of formula (IV):



- 25 or a salt or solvate thereof, wherein R¹, R², R³, R⁴, R⁵, R¹², R¹³, m, and n are as defined for the compound of formula (II) or (III).

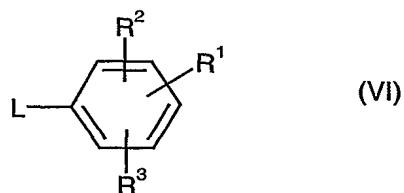
In this process, the group R⁶ should be chosen such that it is sufficiently stable to resist hydrolysis under the conditions required to open the oxazolidine ring in the compound of formula (IV) to give a compound of formula (II) or (III).

- 5 The conversion of a compound of formula (IV) to a compound of formula (II) or (III) may be effected by treatment with a base, for example a non-aqueous base, such as potassium trimethylsilanolate, or an aqueous base such as aqueous sodium hydroxide, in a suitable solvent such as tetrahydrofuran.
- 10 Compounds of formula (IV) may be prepared from the corresponding compound of formula (V):



- 15 or a salt or solvate thereof, wherein R⁴, R⁵, R¹², R¹³, m and n are as defined for the compound of formula (II);

by coupling with a compound of formula (VI) or a precursor thereof:



- 20 wherein R¹, R², and R³ are as defined for the compound of formula (I) or each may independently represent a precursor for said groups, and L is a leaving group, such as a halo group (typically, bromo or iodo) or a haloalkyl sulphonate (typically, trifluoromethanesulphonate), followed by reduction.

The coupling of a compound of formula (V) with a compound of formula (VI) or a precursor thereof is conveniently effected in the presence of a catalyst system such as bis(triphenylphosphine) palladium dichloride with an organic base such as a

5 trialkylamine, for example triethylamine, in a suitable solvent for example acetonitrile or dimethylformamide. The resulting alkyne may then be reduced, either with or without being isolated to form the compound of formula (IV). The reduction may be effected by any suitable method such as hydrogenation in the presence of a catalyst, for example palladium/charcoal or platinum oxide.

10

Compounds of formula (VI) are commercially available or may be prepared by methods well known to the person skilled in the art.

15

A suitable precursor of the compound of formula (VI) would be a compound of formula (VI) in which one or more of the substituents R¹, R², and R³ is a group which is convertible to the desired group R¹, R², and/or R³. For example, when R¹ is to be -XR⁶ and R⁶ is to be the group (a), a suitable precursor of the compound of formula (VI) may have the primary amine in place of the substituent R⁶, such that the desired substituent R¹ may be formed by reaction with an appropriate isocyanate to give an urea group -XNHC(O)NHCH₂C(O)O(C₁₋₆ alkyl). Conversion to the desired group R¹ may then be effected by standing the urea in an inert solvent, optionally in the presence of a base such as an inorganic base, for example potassium carbonate or sodium hydride, or an organic base, for example triethylamine or diisopropylethylamine, either before or after the coupling with the compound of formula (V). Alternatively the urea ester group

20

depicted above may be hydrolysed to the corresponding urea carboxylic acid, followed by treatment with a mineral acid such as hydrochloric acid, or a strong organic acid such as p-toluenesulphonic acid, to give the desired hydantoin group. The primary amine may be formed by reduction of a corresponding nitro group.

25

30

As a further example, when the group R¹ is to be -XR⁶ and R⁶ is to be the group (b), a suitable precursor might have a primary urea in place of the group R⁶, such that the desired substituent R¹ may be formed by reaction with an appropriate compound of

formula $(C_{1-6}\text{alkyl})O_2CCR^8R^9L$, wherein L is a leaving group as in the compound of formula (VI), typically chloro.

As a yet further example, when the group R¹ is to be -XR⁶ and R⁶ is to be the group (c), a suitable precursor might have a formyl group or a group -C(O)R⁸ in place of the group R⁶, such that the desired substituent R¹ may be formed by reaction with NaCN and $(NH_4)_2CO_3$ as in G. Wagner, B. Voigt and I. Lischke, Pharmazie, 1981, **36**, 467.

As a still further example, when the group R¹ is to be -XR⁶ and R⁶ is to be the group (d), a suitable precursor might have a primary amine in place of the group R⁶, such that the desired substituent R¹ may be formed by reaction with an appropriate isocyanate to give a urea group -NHC(O)NHCH₂CH₂L, wherein L is a leaving group as in the compound of formula (VI), typically chloro. Conversion to the desired group R¹ may then be effected by standing the urea in an inert solvent, for example N,N-dimethylformamide, in the presence of a base such as an inorganic base, for example potassium carbonate or sodium hydride, or an organic base, for example triethylamine or diisopropylethylamine, either before or after the coupling with the compound of formula (V).

As another example, if the group R¹ is to be -XR⁶ and R⁶ is to be the group (f), a suitable precursor might have an isocyanate in place of the group R⁶. Conversion to the desired group R⁶ could then be effected by reaction with a masked amino-aldehyde of formula H₂NCH₂CH(OC₁₋₆alkyl)₂ in an inert solvent such as dichloromethane.

Cyclization to the desired R⁶ group could then be effected by unmasking the aldehyde, for example by treatment with an acid such as aqueous trifluoroacetic acid, as in E.R.

Parmee et al., Bioorg. Med. Chem. Lett. 1999, **9**, 749-754.

As a further example , if the group R¹ is to be XR⁶ and R⁶ is to be the group (g) a suitable precursor might have a group -COCH₂NH₂ in place of R⁶. Conversion to the desired group R⁶ may be effected by treating with cyanic acid, according to the procedure described by Rupe, Chem.Ber 1894, **27**, 582.

As another example, if the group R¹ is to be -CH₂R⁶ and R⁶ is to be the group (h), a suitable precursor might have a group Br in place of the group R⁶, such that the desired

5 substituent R¹ may be formed by coupling with the anion derived by deprotonation of parabanic acid or a suitable derivative thereof, for example by treatment with sodium hydride. Alternatively, if the group R¹ is to be -R⁶ and R⁶ is to be the group (h), a suitable precursor might have an iodo group in place of the group R⁶, such that the desired substituent R¹ may be formed by a palladium catalysed condensation with parabanic acid or a suitable derivative thereof.

10 An alternative precursor when R¹ is to be -XR⁶ and R⁶ is to be the group (h) would have a primary urea in place of the group R⁶. Conversion to the desired group R⁶ could then be effected by reaction with (C₁₋₆alkyl)O₂CCOCl.

15 As another example, if the group R¹ is to be XR⁶ and R⁶ is to be the group (i), a suitable precursor might have a group -NHOH in place of the group R⁶. Conversion to the desired group R⁶ could then be effected by reaction with chlorocarbonylisocyanate as in M.S. Malamas et al, Eur. J. Med. Chem. 2001, 36, 31-42.

20 As another example, if the group R¹ is to be XR⁶ and R⁶ is to be the group (j), a suitable precursor might have a group -NHNH₂ in place of the group R⁶. Conversion to the desired group R⁶ could then be effected by reaction with urea in a solvent such as N,N-dimethylformamide, as in J.A. Lenoir and B.L. Johnson, Tetrahedron Letters, 1973, 5123-5126.

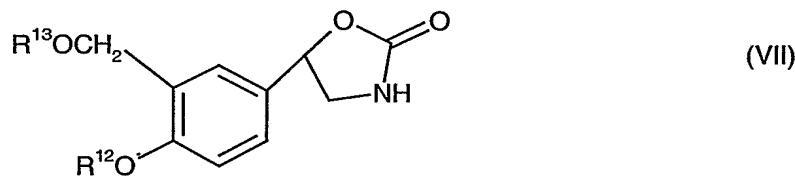
25 As a still further example, when R¹ is to be the group XR⁶ and R⁶ is to be the group (k) a suitable precursor might have an isocyanate in place of the group R⁶ such that the desired substituent R¹ may be formed by treating the isocyanate with hydroxylamine and a chloroformate, eg. an alkyl chloroformate such as ethyl chloroformate, and treating the resulting compound with base, eg. NaOH, to form the desired heterocyclic ring. (G. Zinner and R. Weber, Arch. Pharm. Ber. 1965, 298, 580 – 587).

30 As another example, when the group R¹ is to be XR⁶ and R⁶ is to be the group (l) a suitable precursor might be an isocyanate in place of the group R⁶. This may be treated with an alkyl carbazate eg. ethyl carbazole and the resulting product treated with a base

eg. potassium hydroxide to form the desired heterocycle (W Adam and N Carballeira J. Am. Chem. Soc., 1984, **106**, 2874).

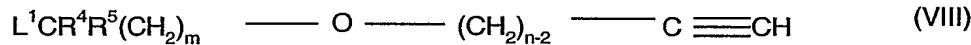
Compounds of formula (V) may be prepared by coupling a compound of formula (VII):

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or a salt or solvate thereof, wherein R¹² and R¹³ are as defined for the compound of formula (V) with a compound of formula (VIII):

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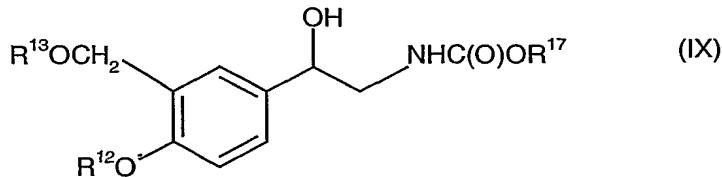


Wherein R⁴, R⁵, m and n are as defined for the compound of formula (V) and L¹ is a leaving group, for example a halo group, (typically bromo or iodo) or a sulphonate such as an alkyl sulphonate (typically methane sulphonate) an aryl sulphonate (typically toluenesulphonate) or a haloalkylsulphonate (typically trifluoromethane sulphonate).

The coupling of a compound of formula (VII) with a compound of formula (VIII) may be effected in the presence of a base, such as a metal hydride, for example sodium hydride, or an inorganic base such as cesium carbonate, in an aprotic solvent, for example N,N-dimethylformamide.

Compounds of formula (VIII) may be prepared from the corresponding dihaloalkane and hydroxyalkyne by conventional chemistry, typically in the presence of an inorganic base, such as aqueous sodium hydroxide, under phase transfer conditions in the presence of a salt such as tetraalkylammonium bromide.

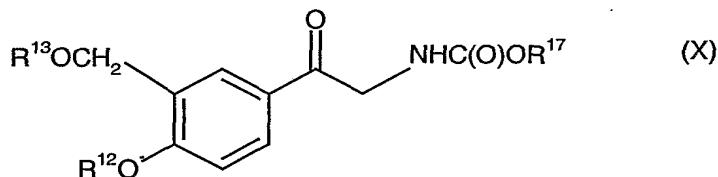
Compounds of formula (VII) may be prepared by ring closure of a compound of formula (IX):



wherein R¹² and R¹³ are as defined for the compound of formula (VII) and R¹⁷ is C₁-

5 alkyl, for example tert-butyl, or aryl, for example phenyl. The ring closure may be effected by treatment with a base, such as a metal hydride, for example sodium hydride, in the presence of an aprotic solvent, for example, N,N-dimethylformamide.

10 Compounds of formula (IX) may be prepared from the corresponding ketone of formula (X):

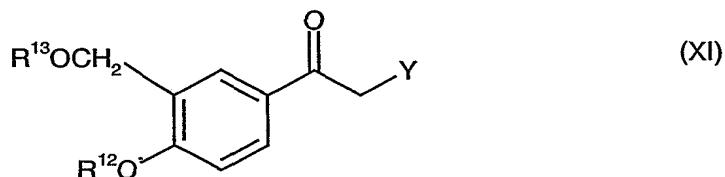


wherein R¹² and R¹³ and R¹⁷ are as defined for the compound of formula (IX), by reduction by any suitable method, for example by treatment with borane, in the

15 presence of a chiral catalyst, such as CBS-oxazaborolidine, in a suitable solvent such as tetrahydrofuran.

The compound of formula (X) may be prepared from the corresponding halide of formula (XI):

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wherein R¹² and R¹³ are as defined for the compound of formula (IV) and Y is a halo, suitably bromo.

The conversion of a compound of formula (XI) to a compound of formula (X) may be

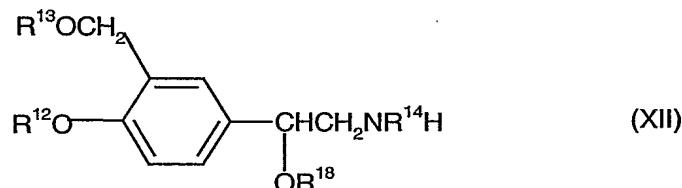
5 effected by reaction with the protected amine HN(COOR¹⁷)₂ wherein R¹⁷ is as defined for the compound of formula (X) in the presence of an inorganic base such as cesium carbonate, followed by selective removal of one of the COOR¹⁷ groups, for example by treatment with an acid such as trifluoroacetic acid.

10 Compounds of formula (XI) may be prepared from the corresponding compound having free hydroxymethyl and hydroxy substituents (which itself may be prepared from 2-bromo-1-(4-hydroxy)-3-hydroxymethyl-phenethyl)ethanone, the preparation of which is described in GB2140800, by treatment with 2-methoxypropane in acetone in the presence of an acid e.g. p-toluenesulphonic acid in a nitrogen atmosphere or by other standard methods) by forming the protected groups R¹³OCH₂- and R¹²O- wherein R¹³ and R¹² are as defined for the compound of formula (XI). Such methods are described 15 in DE 3513885 (Glaxo).

20 Compounds of formulae (II) or (III) where R¹⁴ is hydrogen or a protecting group may be prepared according to the general methods described below.

In a further process (b) a compound of formula (I), (Ia), (Ib) or (Ic) may be obtained by alkylation of an amine of formula (XII):

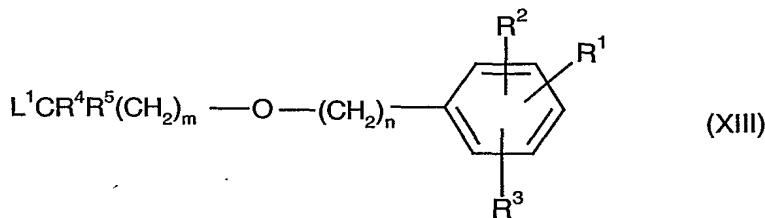
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wherein R¹², R¹³, R¹⁴ and R¹⁸ are each independently either hydrogen or a protecting group. Suitable protecting groups are discussed in the definition of compounds of

30 formula (II) and (III);

with a compound of formula (XIII):



5

wherein R¹, R², R³, R⁴, R⁵, m, and n are as defined for the compound of formula (I), (Ia) or (Ib) and L¹ is a leaving group as herein before defined for the compound of formula (VIII); followed by removal of any protecting groups present by conventional methods as described above for the deprotection of compounds of formula (II) and (III). For speed of reaction, L¹ is preferably bromo or is converted to bromo in situ, from the corresponding compound wherein L¹ is methanesulphonate, for example by addition of tetrabutylammonium bromide to the reaction mixture.

10

The compound of formula (I), (Ia) or (Ib) may be formed directly (when in the compound of formula (XII) R¹², R¹³, R¹⁴ and R¹⁸ are each hydrogen) or via a compound of formula (II) or (III) which may or may not be isolated (when in the compound of formula (XII) at least one of R¹², R¹³, R¹⁴ and R¹⁸ is a protecting group).

15

The reaction of compounds of formulae (XII) and (XIII) is optionally effected in the presence of an organic base such as a trialkylamine, for example, diisopropylethylamine, and in a suitable solvent for example N,N-dimethylformamide, or acetonitrile.

20

Compounds of formula (XII) are known in the art (for example EP-A 0947498) or may be readily prepared by a person skilled in the art, for example from the corresponding halide of formula (XI) as defined above. The conversion of a compound of formula (XI) to a compound of formula (XII) may be effected by reaction with sodium azide in a suitable solvent, for example N,N-dimethylformamide, to give the corresponding compound wherein Y denotes N₃. The carbonyl group may then be reduced to the

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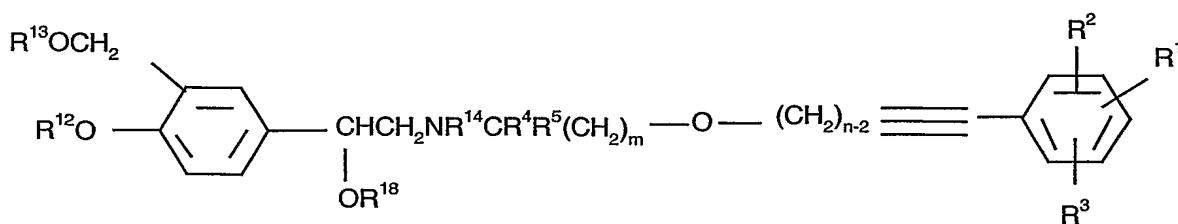
corresponding alcohol by any suitable method, for example by treatment with borane, in the presence of a chiral catalyst, such as (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole, in a suitable solvent such as tetrahydrofuran. The azide group may be reduced to the corresponding amine group by any suitable method,
 5 for example by catalytic hydrogenation in the presence of a catalyst such as palladium/charcoal or platinum oxide.

Compounds of formula (XIII) may be prepared by coupling a compound of formula (VI) or a precursor thereof (wherein one or more of the substituents R¹, R², or R³ is a group
 10 which is convertible to R¹, R², or R³) with a compound of formula (VIII) as shown above, followed by reduction.

The coupling of a compound of formula (VIII) with a compound (VI) may be effected by in the presence of a catalyst system such as bis (triphenylphosphine) palladium
 15 dichloride with an organic base such as a trialkylamine, for example, triethylamine, in a suitable solvent, for example acetonitrile or N,N-dimethylformamide. The resulting alkyne may then be reduced, either with or without being isolated, to form the compound of formula (XIII). The reduction may be effected by any suitable method such as hydrogenation in the presence of a catalyst, for example, palladium/charcoal or
 20 platinum oxide. If necessary, the substituents R¹, R², and/or R³ may be formed by conventional conversions where a precursor is present.

In a yet further process (c) a compound of formula (I), (Ia), (Ib) or (Ic) may be obtained by reduction of a compound of formula (XIV):

25



(XIV)

wherein R¹, R², R³, R⁴, R⁵, m and n are as defined for formula (I) and R¹², R¹³, R¹⁴ and R¹⁸ each independently represent a hydrogen atom or a protecting group as defined above.

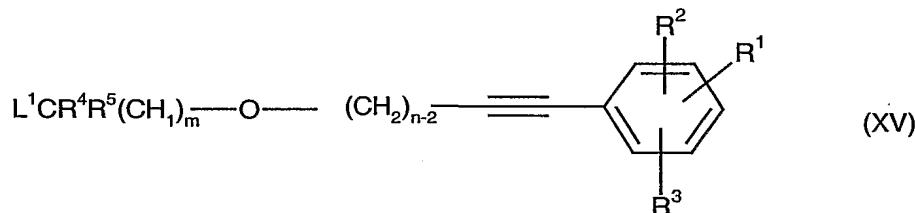
- 5 The reduction may be effected by any suitable method such as hydrogenation in the presence of a catalyst, for example, palladium/charcoal or platinum oxide.

It will be appreciated that where R¹², R¹³, R¹⁴ and R¹⁸ each represent hydrogen, the reduction will yield a compound of formula (I), but where one or more of R¹², R¹³, R¹⁴

- 10 and R¹⁸ represent a protecting group then reduction will yield a compound of formula (II) or (III), which may then be deprotected to give a compound of formula (I).

A compound of formula (XIV) may be prepared by reacting a compound of formula (XII) as herein before defined with a compound of formula (XV):

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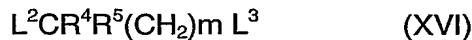


wherein R¹, R², R³, R⁴, R⁵, m, and n are as defined for the compound of formula (I), (Ia) or (Ib) and L¹ is as defined for the compound of formula (XIII).

- 20 The reaction of compounds of formulae (XIV) and (XV) is optionally effected in the presence of an organic base such as a trialkylamine, for example, diisopropylethylamine, and in a suitable solvent for example N,N-dimethylformamide.

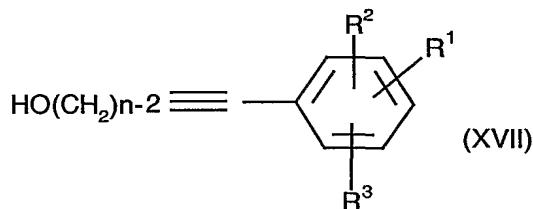
- 25 The compound of formula (XV) may be prepared by coupling a compound of formula (VI) as defined above with a compound of formula (VIII) as defined above, as described for the first stage of the preparation of compounds (XIII), without the reduction step.

An alkyne of formula (XV) may also be prepared by reacting a compound of formula (XVI):



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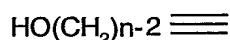
Wherein R^4 , R^5 and n are as defined hereinabove and L^2 and L^3 each represent a leaving group, which groups may independently be selected for example from those defined above for L and L^1 , with a compound of formula (XVII):



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using conventional methods, for example as described for the preparation of compounds (VIII).

Compounds of formula (XVII) may be prepared by reacting a hydroxyalkyne

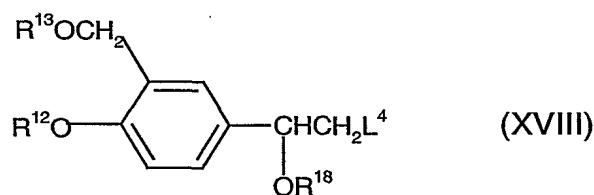


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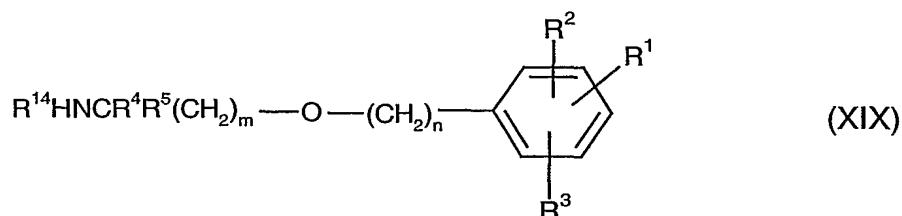
with a compound of formula (VI) using methods analogous to those described above for coupling a compound (V) with a compound (VI).

20

In a further process (d) a compound of formula (I), (Ia), (Ib) or (Ic) may be prepared by reacting a compound of formula (XVIII):



wherein R¹², R¹³ and R¹⁸ are as hereinbefore defined and L⁴ is a leaving group, is reacted with an amine of formula (XIX):



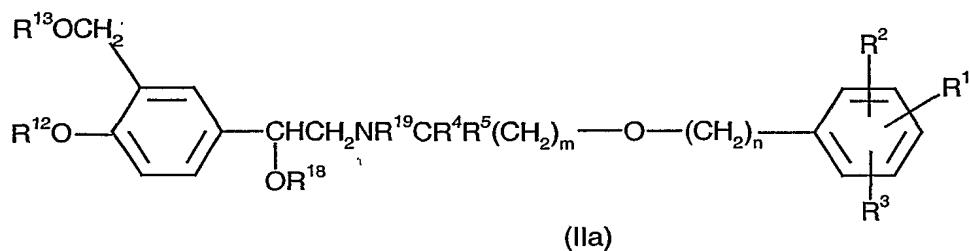
followed by removal of any protecting groups present by conventional methods as described above for the deprotection of compounds of formula (II).

10 The reaction may be effected using conventional conditions for such displacement reactions.

Compounds of formula (XVIII) may be prepared by methods known in the art.

15 Compounds of formula (XIX) may be prepared by reacting a compound of formula (XIII) with an amine R¹⁴NH₂.

In a further process (e) a compound of formula (I), (Ia) or (Ib) may be prepared by removal of a chiral auxiliary from a compound of formula (IIa):



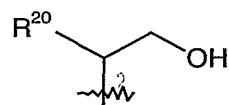
20 wherein R¹, R², R³, R⁴, R⁵, m and n are as defined for formula (I), R¹², R¹³, R¹⁴ and R¹⁸ each independently represent a hydrogen atom or a protecting group as defined above and R¹⁹ represents a chiral auxiliary.

A "chiral auxiliary" is a moiety that is introduced into a molecule to influence the stereochemistry of the product formed, and is removed in whole or part at a later time. A chiral auxiliary may simultaneously function as a protecting group.

- 5 Many chiral auxiliaries are commercially available, and persons skilled in the art would choose one based on the properties desired i.e. the absolute stereochemistry desired and compatibility with the processes being used. Chiral auxiliaries suitable for use in this process include but are not limited to the S-isomer and/or the R-isomer of phenyl glycinol and substituted derivatives thereof.

10

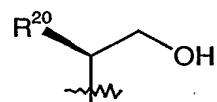
The chiral auxiliary is preferably a moiety of the formula:



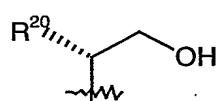
- 15 or a single enantiomer thereof, wherein R²⁰ represents C₁₋₆alkyl or optionally substituted phenyl or benzyl wherein the optional substitution is one or more independently selected from C₁₋₆alkyl, halogen, hydroxy, C₁₋₆alkoxy or nitro e.g. para-hydroxyphenyl.

More preferably the chiral auxiliary is a moiety:

20



wherein R²⁰ is as defined above. Alternatively it may be a moiety of formula:



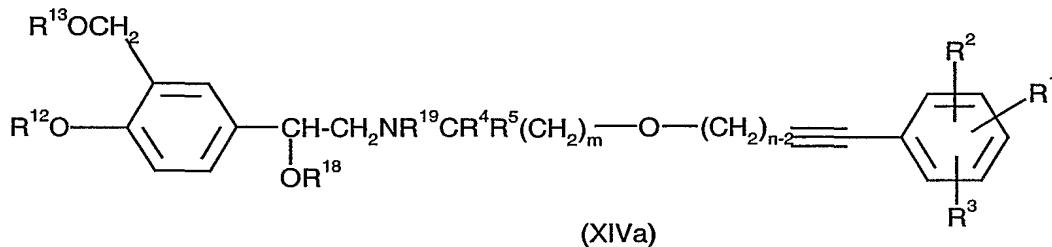
25

wherein R²⁰ is as defined above.

Preferably R²⁰ represents phenyl optionally substituted as described above. Most preferably R²⁰ represents unsubstituted phenyl.

The chiral auxiliary in this process may typically be removed by hydrogenolysis using for example a palladium on carbon catalyst or preferably using palladium hydroxide (Pearlman's catalyst). Advantageously when Pearlman's catalyst is used the removal of the chiral auxiliary is most efficient. This method of removal is especially suitable where R²⁰ is phenyl or a substituted phenyl. Alternatively the nitrogen, to which the auxiliary is attached, may be derivatised under oxidising conditions to form the N-oxide before elimination by heating to give a secondary amine.

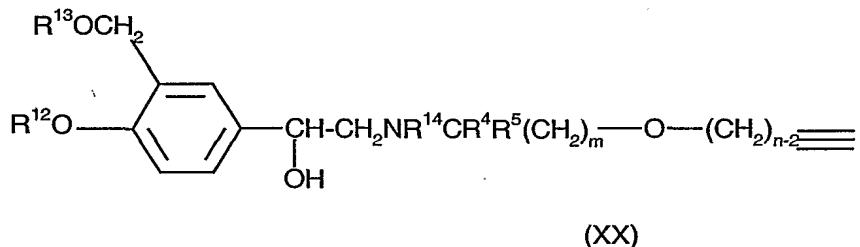
A compound of formula (IIa) may be prepared by reduction of the corresponding alkyne of formula (XIVa):



wherein R¹, R², R³, R⁴, R⁵, m and n are as defined for formula (I) and R¹², R¹³, R¹⁴ and R¹⁸ each independently represent a hydrogen atom or a protecting group as defined above. Preferably in the compounds of formulae (IIa) and (XIVa) the protecting groups R¹² and R¹³ together form a group -CR¹⁵R¹⁶- as in the compounds of formula (III).

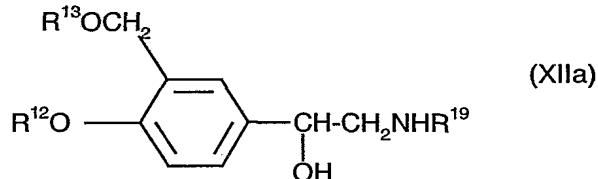
Reduction of an alkyne of formula (XIVa) may be effected by methods well known in the art, for example by catalytic hydrogenation, using palladium on charcoal or more preferably palladium hydroxide (Pearlman's catalyst). The chiral auxiliary may also be removed under reductive conditions. Advantageously, therefore the reduction of the alkyne and removal of the chiral auxiliary may be effected concomitantly in a 'one-pot' reaction.

An alkyne of formula (XIVa) may be prepared by reaction of a compound of formula (XX)



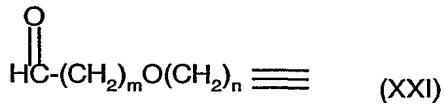
- 5 with a compound of formula (VI) under conditions described above for coupling of compounds (V) and (VI).

A compound of formula (XX) may be prepared by reacting a compound of formula (XIIa):



10

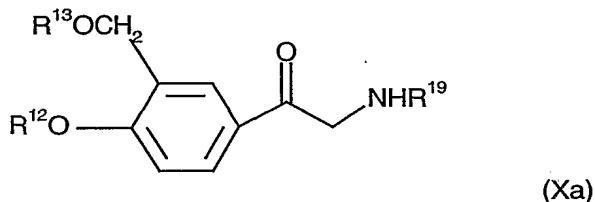
with an aldehyde of formula (XXI):



- 15 using known methods for effecting reductive amination, e.g. sodium triacetoxyborohydride in a solvent such as chloroform

- 20 An aldehyde of formula (XXI) may be prepared from a corresponding halide of formula (VIII) using standard techniques such as treatment with sodium bicarbonate in a solvent such as DMSO at elevated temperature, preferably in the range 130-160°C.

A compound of formula (XIIa) may be prepared from a compound of formula (Xa):



Wherein R¹², R¹³ and R¹⁹ are as hereinbefore defined by treatment with a reducing agent such as a hydride source e.g. sodium borohydride. Preferably this process takes place in the presence of an inert metal salt such as calcium chloride suitably at non-extreme temperatures e.g. below ambient, such as 0°C. This allows the desired stereochemistry to be introduced efficiently with good enantiomeric excess at an early stage in the synthesis, using inexpensive and relatively harmless reagents.

Furthermore, the enantiomeric excess may be increased by recrystallisation of the product of this process.

A compound of formula (Xa) may be prepared from a compound of formula (XI) as hereinbefore defined by reaction with an appropriate chiral amine, e.g. (S)-phenylglycinol, in the presence of a non-nucleophilic base in an inert solvent at non-extreme temperatures.

A detailed description of a process analogous to Route (e) may be found in published International Application Number WO/0196278.

In the above process (e) it is preferred that the protecting groups R¹² and R¹³ together form a protecting group as depicted in formula (III).

It will be appreciated that in any of the routes (a) to (e) described above, the precise order of the synthetic steps by which the various groups and moieties are introduced into the molecule may be varied. It will be within the skill of the practitioner in the art to ensure that groups or moieties introduced at one stage of the process will not be affected by subsequent transformations and reactions, and to select the order of synthetic steps accordingly.

The enantiomeric compounds of the invention may be obtained (i) by separation of the components of the corresponding racemic mixture, for example, by means of a chiral chromatography column, enzymic resolution methods, or preparing and separating suitable diastereoisomers, or (ii) by direct synthesis from the appropriate chiral intermediates by the methods described above.

Optional conversions of a compound of formula (I), (Ia) or (Ib) to a corresponding salt may conveniently be effected by reaction with the appropriate acid or base. Optional conversion of a compound of formula (I), (Ia) or (Ib) to a corresponding solvate or physiologically functional derivative may be effected by methods known to those skilled in the art.

According to a further aspect, the present invention provides novel intermediates for the preparation of compounds of formula (I), (Ia) or (Ib), for example: compounds of formula (II), (III) and XIV as defined above, or an optical isomer, a salt, or a protected derivative thereof; particularly, a compound selected from:

3-(3-{4-[(6-{[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)imidazolidine-2,4-dione;
3-(3-{3-[(7-{[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}heptyl)oxy]propyl}phenyl)imidazolidine-2,4-dione;
1-(3-{4-[(6-{[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)imidazolidin-2-one; and
1-(3-{4-[(6-{[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)imidazolidine-2,4-dione;
3-(3-{4-[(6-{[(2S)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)imidazolidine-2,4-dione;
3-(4-{4-[(6-{[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)imidazolidine-2,4-dione;
3-(2-{4-[(6-{[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)imidazolidine-2,4-dione;

- 3-(3-{4-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}benzyl)imidazolidine-2,4-dione;
3-(3-{5-[(5-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}pentyl)oxy]pentyl}phenyl)imidazolidine-2,4-dione;
- 5 3-(3-{5-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]pentyl}phenyl)imidazolidine-2,4-dione;
3-(3-{6-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]hexyl}phenyl)imidazolidine-2,4-dione;
3-(3-{6-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]hexyl}phenyl)imidazolidine-2,4-dione;
- 10 (5*S*)-5-(3-{4-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}benzyl)-5-methylimidazolidine-2,4-dione;
2-[3-(3-{4-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)-2,4-dioxoimidazolin-1-yl]acetamide;
- 15 5-{4-[4-[(6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl)oxy]butyl}benzyl}imidazolidine-2,4-dione;
3-(3-{4-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)-5,5-dimethylimidazolidine-2,4-dione;
3-(3-{3-[(7-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-
- 20 hydroxyethyl]amino}heptyl)oxy]propyl}phenyl)-1-(methylsulfonyl)imidazolidine-2,4-dione;
1-(3-{3-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]propyl}phenyl)imidazolidine-2,4-dione;
N-[1-(3-{4-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}benzyl]-2,5-dioxoimidazolin-4-yl]urea;
- 25 3-Benzyl-1-(3-{4-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)imidazolidine-2,4-dione;
1-(3-{4-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)-3-methylimidazolidine-2,4-dione;
Ethyl [3-(3-{4-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-
- 30 hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)-2,5-dioxoimidazolin-1-yl]acetate;
2-[3-(3-{4-[(6-[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)-2,5-dioxoimidazolin-1-yl]acetamide;

1-(3-{4-[(6-{[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}benzyl)imidazolidine-2,4-dione;
3-Benzyl-1-(3-{4-[(6-{[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)imidazolidine-2,4-dione;
5 3-(3-{4-[(6-{[(2R)-2-(2,2-imethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)-1-(methylsulfonyl)imidazolidine-2,4-dione;
and
4-(3-{4-[(6-{[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)-1,2,4-triazolidine-3,5-dione.

10

For a better understanding of the invention, the following Examples are given by way of illustration.

SYNTHETIC EXAMPLES

15 Throughout the examples, the following abbreviations are used:

LCMS: Liquid Chromatography Mass Spectrometry

MS : mass spectrum

TSP+ve : thermospray mass spectrum positive mode

HPLC: high pressure liquid chromatography

20 RT : retention time

THF : tetrahydofuran

DMF : N,N-dimethylformamide

EtOAc : ethyl acetate

Et₂O : diethyl ether

25 EtOH : ethanol

MeOH : methanol

bp : boiling point

ca : circa

h : hour(s)

30 min : minute(s)

All temperatures are given in degrees centigrade.

Silica gel refers to Merck silica gel 60 Art number 7734.

Flash silica gel refers to Merck silica gel 60 Art number 9385.

Biotage refers to prepacked silica gel cartridges containing KP-Sil run on flash 12i chromatography module.

Bond Elut are prepacked cartridges used in parallel purifications, normally under vacuum. These are commercially available from Varian.

5

LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% HCO₂H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO₂H 5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 min 0%B, 0.7-4.2 min 100%B, 4.2-5.3 min 0%B, 5.3-5.5 min 0%B at a flow rate of 3 ml/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

10

HPLC was conducted on a LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% formic acid and 0.01 M ammonium acetate in water (solvent A), and 0.05% formic acid 5% water in acetonitrile (solvent B) using the following elution gradient 0-1 min 0%B, 1-10 min 100%B, 10-13 min 100%B, 13-15 min 0%B at a flow rate of 1ml/min detecting at 215 to 330 nm.

15

20

Example 1: 3-[3-(4-{[6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy]butyl]phenyl]imidazolidine-2,4-dione acetate

i) 6-Bromohexyl but-3-ynyl ether

25

30

3-Butyn-1-ol (42.4ml) was stirred vigorously with 1,6-dibromohexane (260ml) and tetrabutylammonium bisulphate (2.4g) in 50% aqueous sodium hydroxide solution (200ml) under nitrogen for 3 days. Water (ca 700ml) was added and the organic layer was separated. The aqueous layer was extracted twice with dichloromethane (2 x 100ml) and the combined organic layers were washed with water, dried (MgSO₄) and concentrated. The residue in petroleum ether (bp 40 - 60°) was loaded onto a column of silica gel (1.5kg) and the column was eluted with petroleum ether (bp 40 - 60°), then 10% diethyl ether in petroleum ether (bp 40 - 60°) to give the *title compound* (103.3g).

ii) 1-{4-[(6-Bromohexyl)oxy]but-1-ynyl}-3-nitrobenzene

A mixture of 1-iodo-3-nitrobenzene (3g), 6-bromohexyl but -3-ynyl ether (3g), bis(triphenylphosphine)palladium (II) chloride (0.421g), copper (I) iodide (0.114g) in DMF (10ml) and diisopropylethylamine (4ml) was stirred under nitrogen at 20 °C for 5h.

- 5 The mixture was concentrated under reduced pressure and the residue was diluted in EtOAc and washed with 2M HCl, NaHCO₃, brine and dried (MgSO₄). The solvent was removed by evaporation and the residue was chromatographed on a Biotage column eluting with ether:petroleum ether(40-60°C) (1:9) to give *the title compound* (4.12g). LCMS RT=4.14min

10

iii) 6-{[4-(3-Nitrophenyl)but-3-ynyl]oxy}hexyl acetate

A mixture of 1-{4-[(6-bromohexyl)oxy]but-1-ynyl}-3-nitrobenzene (4.18g), sodium acetate (9.68g), tetrabutylammonium bromide (384mg) in DMF (15ml) and water (10ml) was heated to 75°C for 6h. The mixture was then allowed to cool to 20°C and then extracted with Et₂O. The organic solution was concentrated and purified by chromatography on a Biotage (40g) eluting with Et₂O-petroleum ether(1:19 increasing to 1:1) to give *the title compound* (2.973g). LCMS RT=3.84min.

iv) 6-[4-(3-Aminophenyl)butoxy]hexyl acetate

- 20 6-{[4-(3-Nitrophenyl)but-3-ynyl]oxy}hexyl acetate (2.973g) was hydrogenated over PtO₂ (300mg) in EtOH over 1h. The catalyst was removed by filtration and washed with EtOH. The combined filtrate and washings were concentrated under reduced pressure to give *the title compound* (2.844g) LCMS RT=3.30min.

- 25 v) Ethyl N-({[3-(4-[(6-(acetyloxy)hexyl)oxy]butyl)phenyl]amino}carbonyl)glycinate
6-[4-(3-Aminophenyl)butoxy]hexyl acetate (2.84g) in CH₂Cl₂ (30ml) was treated with ethyl isocyanatoacetate (1.2ml). After 0.75h the mixture was treated with MeOH (2ml) and stirred for 0.5h. The mixture was concentrated, purified on a 10g silica Bond Elut cartridge eluting with Et₂O-petroleum ether(1:1) and then with Et₂O to give *the title compound* (3.33g) ES+ve 437 (MH)⁺.

vi) 3-(3-{4-[(6-Hydroxyhexyl)oxy]butyl}phenyl)imidazolidine-2,4-dione

A solution of ethyl N-({[3-(4-{[6-(acetoxy)hexyl]oxy}butyl)phenyl]amino}- carbonyl)glycinate (2.967g) in ethanol (30ml) was treated under nitrogen with sodium hydride (60% oil dispersion; 280mg) and the mixture was stirred for 18h. The solvent was removed under reduced pressure, the residue was dissolved in acetic acid (10ml) 5 and conc. HBr (1ml) and the mixture was heated to 75°C for 1h. The solvent was removed under reduced pressure, the residue was partitioned between EtOAc and brine. The organic solution was washed with brine, dried and evaporated to dryness. The residue was dissolved in MeOH (30 ml), SOCl₂ (0.5ml) was added, and the solution 10 was stirred for 2h. The solvent was removed under reduced pressure to give *the title compound* (2.67g) ES+ve 349 (MH)⁺.

vii) 6-[4-[3-(2,5-Dioxoimidazolidin-1-yl)phenyl]butoxy]hexyl methanesulfonate
3-(3-{4-[{(6-Hydroxyhexyl)oxy}butyl]phenyl}imidazolidine-2,4-dione (2.67g) in CH₂Cl₂ (50ml) and triethylamine (1.2ml) was treated with methanesulfonyl chloride (1.22ml) and 15 the mixture was stirred at 20°C for 1.5h. The mixture was diluted with CH₂Cl₂ and washed with 2M HCl, NaHCO₃, dried and purified by chromatography on Biotage (40g) eluting with EtOAc-petroleum ether(1:1) and then with 2% MeOH-CH₂Cl₂ to give *the title compound* (1.186g) ES+ve 427 (MH)⁺.

viii) 2-Azido-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanone
2-Bromo-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanone (Glaxo DE 3513885, 1985) (52g) in DMF (300ml) was treated with sodium azide (12.24g) and the mixture was 20 stirred for 2h at 20°C. The reaction mixture was diluted with EtOAc and washed with water and dried (MgSO₄). The solvent was removed under reduced pressure to give 25 *the title compound* (39.11g). TSP+ve 248(MH)⁺.

ix) (1R)-2-Azido-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol
(R)-Tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole solution in toluene (1M, 7.5ml) was added to THF (75ml) and the solution was diluted to 0°C. 30 Borane-THF complex (1M solution in THF, 125ml) was added and the mixture was stirred under nitrogen for 15min. A solution of 2-azido-1-(2,2-dimethyl-4H-1,3- benzodioxin-6-yl)ethanone (24.7g) in THF (250ml) was added dropwise over 1.5h at 5°C. The mixture was stirred for a further 1h and then cautiously treated with 2M HCl

(100ml). The reaction mixture was extracted with ether and the organic layer was washed with 2M HCl, NaHCO₃, brine, dried (MgSO₄). The solvent was removed by evaporation and the residue was chromatographed on a Biotage column eluting with ether-petroleum ether(40-60°C) (1:9; 1:1) to give *the title compound* (16.99g). ES+ve 5 250 (MH)⁺.

x) (1R)-2-Amino-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol

(1R)-2-Azido-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol (16.99g) was hydrogenated over 10% Pd-C (1g) in EtOH (300ml). The catalyst was collected by 10 filtration, and washed with EtOH. The combined washings were evaporated under reduced pressure and the residue was triturated in ether to give *the title compound* (5.86g). The mother liquors were chromatographed on a Biotage column eluting with toluene:EtOH:aqueous ammonia (85:14:1) to give a further batch of *the title compound* (5.99g). LCMS RT=1.68 min, ES+ve 206 (MH-H₂O)⁺.

15

xi) 3-(3-{4-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl]phenyl)imidazolidine-2,4-dione

A solution of 6-{4-[3-(2,5-dioxoimidazolidin-1-yl)phenyl]butoxy}hexyl methanesulfonate (766mg) in DMF (8ml) was treated with tetrabutylammonium bromide (578mg) and 20 (1R)-2-amino-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol (544mg) and the mixture was stirred at 20°C for 3d. The solvent was removed under reduced pressure, the residue was dissolved in CH₂Cl₂, washed with water and purified by chromatography on Biotage (40g) eluting with 3% 2M NH₃ in MeOH:CH₂Cl₂ to give *the title compound* (417mg). ES+ve 554 (MH)⁺

25

xii) 3-[3-(4-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino}hexyl)oxy]butyl]phenyl)imidazolidine-2,4-dione acetate

A solution of 3-(3-{4-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl]phenyl)imidazolidine-2,4-dione (414mg) in acetic acid (20ml) and water (5ml) was heated to 75 °C for 30min before evaporating to dryness. The residue was purified by chromatography on Biotage (40g) eluting with CH₂Cl₂:MeOH:2M NH₃ in MeOH (85:10:5). Appropriate fractions were combined and

evaporated to dryness. Acetone (10ml) was added and the mixture was re-evaporated under reduced pressure to give *the title compound* (290mg). LCMS RT=2.44min, ES+ve 514 (MH)⁺.

1H NMR (DMSO+D₂O) 7.36 (1H, t, J 8 Hz), 7.28 (1H, br s), 7.20 (1H, d, J 8 Hz), 7.10 (1H, s), 7.09 (1H, d, J 8 Hz), 7.04 (1H, dd, J 8, 2 Hz), 6.73 (1H, d, J 8 Hz), 4.73 (1H, dd, J 5, 8 Hz), 4.45 (2H, s), 4.08 (2H, s), 3.33 and 3.30 (2H each, t, J 7 Hz), 2.98-2.90 (2H, m), 2.86 (2H, t, J 7 Hz), 2.59 (2H, t, J 7 Hz), 1.85 (3H, s), 1.62-1.4 (8H, m), 1.3-1.2 (4H, m)

10 **Example 2:** 3-[3-(3-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)heptyl]oxy]propyl]phenyl]imidazolidine-2,4-dione acetate

i) 1-{3-[(7-Bromoheptyl)oxy]prop-1-ynyl}-3-nitrobenzene

15 was prepared using methods similar to those described in Example 1ii).

tlc Rf 0.21 (5% Et₂O/petrol)

ii) 7-[(3-Nitrophenyl)prop-2-ynyl]oxy}heptyl acetate

was prepared using methods similar to those described in Example 1iii).

20 LCMS RT=3.78min

iii) 7-[3-(3-Aminophenyl)propoxy]heptyl acetate

was prepared using methods similar to those described in Example 1iv).

LCMS RT=3.38min

25 iv) Ethyl N-((3-(3-[(7-(acetyloxy)heptyl]oxy)propyl]phenyl]amino)carbonyl)glycinate

was prepared using methods similar to those described in Example 1v).

LCMS RT=3.52min

30 v) 3-(3-[3-[(7-Hydroxyheptyl)oxy]propyl]phenyl)imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 1vi).

ES+ve 349 (MH)⁺.

vi) 7-[3-[3-(2,5-dioxoimidazolidin-1-yl)phenyl]propoxy]heptyl methanesulfonate was prepared using methods similar to those described in Example 1vii).
ES+ve 427 (MH)⁺.

5 vii) 3-(3-[3-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino]heptyl)oxy[propyl]phenyl)imidazolidine-2,4-dione formate was prepared using methods similar to those described in Example 1xi).
ES+ve 554 (MH)⁺.

10 viii) 3-[3-(3-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)heptyl]oxy[propyl]phenyl)imidazolidine-2,4-dione acetate
was prepared using methods similar to those described in Example 1xii).
LCMS RT=2.39min, ES+ve 514 (MH)⁺.

15 **Example 3:** 1-[3-(4-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]butyl)phenyl)imidazolidin-2-one acetate

20 i) Di(tert-butyl) 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylimidodicarbonate
Caesium carbonate (70.4g) was added to a stirred suspension of 2-bromo-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanone, (Glaxo, DE 3513885, 1985) (61.8g) and di-t-butyl iminodicarboxylate (47.15g) in acetonitrile (600ml) under nitrogen. After vigorous stirring at 21° for 24 h the mixture was diluted with water (ca800ml) and the product was extracted with diethyl ether (1litre, then 200ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to ca400ml. The white crystals were collected by filtration, washed with diethyl ether and dried to give the *title compound* (24.4g) δ ($CDCl_3$) 7.78(1H, dd, J 8, 2Hz), 7.65 (1H, brs), 6.87(1H, d, J 8Hz), 4.97(2H, s), 4.88(2H, s), 1.56(6H, s) and 1.48 (18H, s) . Further concentration of the mother liquors gave additional product (13.8g). A third crop (7.1g) was obtained by chromatographing the mother liquors on silica gel, evaporating the appropriate eluate and triturating with diethyl ether.

25 ii) tert-Butyl 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylcarbamate

30

Trifluoroacetic acid (92ml) was added to a stirred solution of di(tert-butyl) 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylimidodicarbonate, (352.55g) in dichloromethane (3.6litres) at 21° and the reaction was stirred for 1.5 h. Aqueous NaOH solution (1.75litres) was added and after 10 min the phases were separated.

- 5 The organic layer was washed with water, dried (MgSO_4) and evaporated to an oil. This was stored under high vacuum overnight and then triturated with hexane:ether (3:1) to give the crude product (226.61g). This was purified by recrystallisation from diethyl ether to give the *title compound* (122.78g). Further product (61.5g) was obtained from the mother liquors by evaporation and chromatography on a Biotage using 15% ethyl acetate in hexane. LCMS RT = 3.37min.
- 10

iii) tert-Butyl (2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethylcarbamate

- A 2M solution of borane - dimethyl sulphide in THF (28ml) was added slowly to a 1M solution of (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole in toluene (56ml) at 0° under nitrogen. A solution of tert-butyl 2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxoethylcarbamate, (108.2g) in THF (1.3litres) was added slowly keeping the temperature below 5° followed by 2M solution of borane - dimethyl sulphide in THF (252ml) over 50 min. After 1 h, 2M HCl (170ml) was added with cooling and the mixture was partitioned between ethyl acetate and water . The organic layer was washed with saturated NaHCO_3 solution and brine and dried (MgSO_4). The solution was concentrated and the product purified by chromatography on flash silica gel (800g), eluting successively with hexane:ethyl acetate (4:1 then 3:1) to give the *title compound* (93.3g), LCMS RT = 3.31min.
- 15
- 20

- 25 iv) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one
tert-Butyl (2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethylcarbamate, (86.37g) in DMF (600ml) was added dropwise to a stirred suspension of sodium hydride (60% oil dispersion, 11.9g) in DMF (160ml) with cooling such that the internal temperature remained at 0° under nitrogen. The mixture was stirred at 21° for 2 h. The mixture was recooled to 0° and 2M HCl (134ml) was added. The mixture was diluted with water and the product was extracted with ethyl acetate twice. The solution was washed with brine twice, dried (MgSO_4) and evaporated to give the *title compound* (63.55g) LCMS RT = 2.66min.
- 30

v) 6-Bromohexyl but-3-yne-1-yl ether

was prepared as described in Example 1(i).

5 vi) (5R)-3-[6-(But-3-ynyloxy)hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (10g) in DMF (100ml) was added dropwise to a stirred suspension of sodium hydride (60% oil dispersion, 2.33g) in DMF (50ml) with stirring under nitrogen and maintaining the internal temperature at 0°. Stirring was continued at 0 - 5° for 1 h. The mixture was recooled to 0° and a solution of 6-bromohexyl but-3-yne-1-yl ether (14.7g) in DMF (50ml) was added over 1 min. The mixture was then stirred at 20 - 30° for 2 h. 2M HCl (9ml) was added and the mixture was partitioned between water and diethyl ether. The aqueous layer was extracted with more diethyl ether and the combined organic layers were washed twice with brine. After drying ($MgSO_4$) the solution was concentrated and loaded onto a column of silica gel (600g) set up in diethyl ether: petroleum ether (bp 40 - 60°) (1:2). The column was eluted successively with this mixture, then (1:1) and then diethyl ether to give the *title compound* (13.88g) LCMS RT = 3.45min.

20 vii) 1-(3-Iodophenyl)imidazolidin-2-one

A solution of 3-iodoaniline (1g) in CH_2Cl_2 (5ml) and diisopropylethylamine (2ml) was treated with 2-chloroethylisocyanate (0.4ml) and the mixture was stirred at 20°C for 3d. The mixture was diluted with EtOAc and washed with 2M HCl, dried and evaporated to dryness. The residue was dissolved in DMF (5ml), treated with sodium hydride (60% oil dispersion, 182mg), and the mixture was stirred for 20h under nitrogen. The mixture was diluted with EtOAc, washed with 2M HCl, brine, dried and evaporated to dryness. The residue was crystallised from hot EtOAc/MeOH. Trituration in Et_2O of the residue obtained by evaporation of the mother liquor gave the *title compound* (240mg). LCMS RT=3.03min.

30

viii) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-[6-(4-[3-(2-oxoimidazolidin-1-yl)phenyl]but-3-ynyl)oxy]hexyl]-1,3-oxazolidin-2-one

(5R)-3-[6-(But-3-ynyloxy)hexyl]-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (376mg) was stirred with 1-(3-iodophenyl)imidazolidin-2-one (250mg) in DMF (10ml) and diisopropylethylamine (3ml) under nitrogen for 10min.

Dichlorobis(triphenylphosphine)palladium (30mg) and cuprous iodide (8mg) were added and the mixture was stirred for 17h under nitrogen at 20 °C. The mixture was evaporated to dryness and the residue was chromatographed on Biotage (40g) eluting with EtOAc–petroleum ether (bp 40–60°C) (1:1) and then on two preparative plates (20 × 20 cm) eluting with MeOH-CH₂Cl₂ (1:19) to give *the title compound* (120mg). LCMS RT=3.49min

10

ix) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-(6-{4-[3-(2-oxoimidazolidin-1-yl)phenyl]butoxy}hexyl)-1,3-oxazolidin-2-one

(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-[6-{4-[3-(2-oxoimidazolidin-1-yl)phenyl]but-3-ynyl}oxy]hexyl)-1,3-oxazolidin-2-one (120mg) was hydrogenated over platinum oxide (54mg) in EtOH (100ml). The catalyst was removed by filtration and the residue was leached with EtOH. The combined filtrates were evaporated under reduced pressure to give *the title compound* (113mg). LCMS RT=3.55min

15

x) 1-(3-{4-[6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy}butyl)phenyl)imidazolidin-2-one

(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-(6-{4-[3-(2-oxoimidazolidin-1-yl)phenyl]butoxy}hexyl)-1,3-oxazolidin-2-one (113mg) was stirred in THF (8ml) while purging with a vigorous stream of nitrogen for 3min. Potassium trimethylsilanolate (285mg) was added and the mixture was stirred at 80°C under nitrogen for 0.75h.

20

MeOH (10ml) was added and then the solvents were removed under reduced pressure. The residue was dissolved in MeOH and applied to a silica Bond Elut cartridge (10g) which was pre-conditioned in CH₂Cl₂ eluting with CH₂Cl₂, 5% MeOH-CH₂Cl₂, 2% increasing to 10% 2M NH₃ in MeOH-CH₂Cl₂ to give *the title compound* (39mg). LCMS RT=2.94min

25

xi) 1-[3-(4-[6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino}hexyl)oxy}butyl)phenyl]imidazolidin-2-one acetate

was prepared using methods similar to those described in Example 1xii). LCMS RT=2.47min, ES+ve 500 (MH)⁺

Example 4: 1-[3-(4-{{(2R)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl]phenyl]imidazolidine-2,4-dione
formate

i) 1-(3-iodophenyl)imidazolidine-2,4-dione

A solution of 3-iodophenylurea (2.1g) in DMF (20ml) was treated with sodium hydride (60% oil dispersion; 640 mg), followed by ethyl chloroacetate (0.93ml) and the mixture was stirred for 5h. The mixture was partitioned between EtOAc and 2M HCl and the organic solution was washed with NaHCO₃, brine, dried and evaporated to dryness to give the *title compound* (2.08g)

ES+ve 303(MH)⁺.

15

ii) 1-{3-[4-((6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)but-1-ynyl]phenyl]imidazolidine-2,4-dione}

was prepared using methods similar to those described in Example 3vi).

LCMS RT=3.63min

20

iii) 1-{3-[4-((6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)butyl]phenyl]imidazolidine-2,4-dione}

was prepared using methods similar to those described in Example 3vii).

LCMS RT=3.53min

25

iv) 1-(3-{4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy}butyl]phenyl]imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 3viii).

LCMS RT=2.98min

30

v) 1-[3-(4-{{(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl]phenyl]imidazolidine-2,4-dione
formate

was prepared using methods similar to those described in Example 1xii). The crude product was purified on HPLC eluting with a gradient of MeCN-H₂O-HCO₂H to give *the title compound*. LCMS RT=2.53min, ES+ve 514 (MH)⁺.

5 **Example 5: 3-[3-(4-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]butyl]phenyl]imidazolidine-2,4-dione acetate**

i) Ethyl N-[(3-iodophenyl)amino]carbonyl]glycinate

10 A solution of 3-idoaniline (9.39g) in dichloromethane (75ml) was treated with ethyl isocyanatoacetate (7.21ml) at 0°C and the mixture was stirred for 2h and allowed to warm to 20°C. EtOH (10ml) was added and the mixture was stirred for 15h. The solvents were evaporated under reduced pressure and the residue was triturated in Et₂O to give *the title compound* (12.9g)LCMS RT=3.08min.

15 ii) 3-(3-Iodophenyl)imidazolidine-2,4-dione

A solution of ethyl N-[(3-iodophenyl)amino]carbonyl]glycinate (9.42g) in DMF (60ml) was treated with sodium hydride (60% oil dispersion, 1.2g) at 20 °C. After 2h the reaction mixture was treated with aqueous 2M HCl (200ml) and stirred overnight. The 20 solid was collected by filtration, washed with water and dried to give *the title compound* (6.9g) LCMS RT=2.45min.

iii) 3-(3-{4-[(6-Bromohexyl)oxy]but-1-ynyl}phenyl)imidazolidine-2,4-dione

25 A mixture of 3-(3-iodophenyl)imidazolidine-2,4-dione (0.75g), 6-bromohexyl but-3-ynyl ether (1.3g), bis(triphenylphosphine)palladium dichloride (87mg) in DMF (10ml) was treated with diisopropylethylamine (3ml) and copper (I) iodide (23mg) and the mixture was stirred for under nitrogen for 24h. The solvents were removed under reduced pressure, the residue was diluted with EtOAc and washed with aqueous 2M HCl, aqueous dilute ammonia, brine and dried (MgSO₄). The solvent was removed under 30 reduced pressure and the residue was purified on two Bond Elut 10g silica cartridges eluting with dichloromethane, Et₂O, and EtOAc to give *the title compound* (760mg) together with 3-(3-{4-[(6-iodohexyl)oxy]but-1-ynyl}phenyl)imidazolidine-2,4-dione (760mg, 22:3).

iv) 3-(3-{4-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]but-1-ynyl}phenyl)imidazolidine-2,4-dione

A mixture of 3-(3-{4-[(6-bromohexyl)oxy]but-1-ynyl}phenyl)imidazolidine-2,4-dione and

5 3-(3-{4-[(6-iodohexyl)oxy]but-1-ynyl}phenyl)imidazolidine-2,4-dione (760mg, 22:3), (1*R*)-2-amino-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol (800mg) in DMF (5ml) was stirred at 20°C for 22h. The solvent was removed under reduced pressure and the residue was diluted with EtOAc and washed with water, brine and dried ($MgSO_4$). The solution was concentrated and purified by chromatography on Biotage (40g) eluting with dichloromethane:MeOH:1M ammonia in methanol (98:1:1 to 95:4:1) to give *the title compound* (368mg) LCMS RT=2.59min.

10 v) 3-(3-{4-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl)imidazolidine-2,4-dione

15 A solution of 3-(3-{4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]but-1-ynyl}phenyl)imidazolidine-2,4-dione (368mg) was hydrogenated over platinum oxide (100mg) in EtOAc (100ml) over 3h. The catalyst was collected by filtration, washed with EtOAc and EtOH. The combined filtrate and washings were evaporated under reduced pressure to give the title compound LCMS

20 RT=2.55min

vi) 3-[3-(4-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]butyl}phenyl)imidazolidine-2,4-dione acetate

25 was prepared using methods similar to those described in Example 1xii
LCMS RT=2.38min, ES+ve 514(MH^+).

Example 6: 3-[3-(4-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]butyl}phenyl)imidazolidine-2,4-dione acetate

(i) (1R) 2-Bromo-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol

A solution R-diphenylprolinol (75mg) in THF (2ml) was treated with borane-THF (1M, 20.5ml) over 20 min at 20°C under nitrogen. After the addition was complete the solution was kept between 30 and 35°C for 1h and then cooled in ice and 2-bromo-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanone (DE3513885) (3.9g) in THF (10ml) was 5 added over 1.5h keeping the temperature below 5°C. The mixture was stirred under nitrogen for a further 0.5h and then methanol (4ml) was added at 0°C. The solvent was removed under reduced pressure and the residue was purified by chromatography on flash silica gel eluting with ethyl acetate-cyclohexane (1:4) to give the *title compound* (3.31g) δ (CDCl₃) 7.15 (1H, dd, J 8, 2 Hz), 7.03 (1H, br s), 6.82 (1H, d, J 8 Hz), 4.85 10 (3H, s and m), 3.61 (1H, dd, J 10, 4 Hz), 3.50 (1H, dd, J 10, 9 Hz), 1.54 (6H, s).

(ii) {[(1*R*)-2-Bromo-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethyl]oxy}(triethyl)silane
Triethylsilyl chloride (205g) was added dropwise to a stirred mixture of (1*R*)-2-Bromo-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol (350g) and imidazole (108.5g) in DMF 15 (875ml) at 5°C. Upon complete addition the mixture was warmed to 15°C and stirred, at this temperature for 1 h. n-Hexane (3500ml) was then added to the mixture which was washed with water (3x1750ml). The organic layer was dried over anhydrous MgSO₄ before being filtered and concentrated under reduced pressure to give the *title compound* (488.6g) as an oil, δ (DMSO-d₆) 7.18 (1H, d, J 8.2Hz), 7.10 (1H, s), 6.75 20 (1H, d, J 8.2Hz), 4.83 (1H, m), 4.78 (2H, d, J 6.9Hz), 3.55 (2H, m), 1.45 (6H, s), 0.84 (9H, t, J 8.1Hz), 0.51 (6H, m).

(iii) *N*-Benzyl-*N*-{(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-
[(triethylsilyl)oxy]ethyl}amine
A mixture of {[(1*R*)-2-bromo-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethyl]oxy}(triethyl)silane (130g) and benzylamine (177ml) in 1,4-dioxane (650ml) was heated at 105°C with stirring overnight. The mixture was then cooled to room 25 temperature and water (150ml) and diethyl ether (1200ml) added. The layers were separated and the ethereal layer was washed with saturated ammonium chloride solution (3x600ml), saturated sodium bicarbonate solution (200ml) and then brine (200ml). The solution was dried over anhydrous Na₂SO₄ before being filtered and 30 concentrated under reduced pressure to give the *title compound* (129.9g) as an oil, δ (CDCl₃) 7.22 (5H, m), 7.02 (1H, d, J 8.7Hz), 6.86 (1H, s), 6.68 (1H, d, J 8.3Hz), 4.75

(2H, s), 4.69 (1H, m), 3.73 (2H, s), 2.70 (2H, m), 1.46 (6H, s), 0.79 (9H, m), 0.44 (6H, m).

iv) (1*R*)-2-(Benzylamino)-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol

5 Tetrabutylammonium fluoride (395ml, 1M in THF) was added dropwise to a stirred solution of *N*-benzyl-*N*-(*2R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-[triethylsilyl]oxy]ethyl]amine (129.9g) in THF (900ml) at 5°C. Upon complete addition the reaction mixture was maintained at this temperature for 15min before water (600ml) was added. The resulting slurry was diluted with diethyl ether (500ml) and filtered. The 10 filtrate was washed with water (2x500ml) and brine (500ml) before being dried over anhydrous Na₂SO₄. The resulting mixture was filtered and concentrated under reduced pressure to give a solid which was triturated with diisopropyl ether to give the *title compound* (70g) as a solid, δ (CDCl₃) 7.31 (5H, m), 7.09 (1H, d, J 8Hz), 6.98 (1H, s), 6.77 (1H, d J 8Hz), 4.82 (2H, s), 4.63 (1H, m), 3.83 (2H, d, J 4Hz), 2.80 (2H, m), 1.52 (6H, s).

15

v) 3-(3-{4-[(6-{Benzyl}[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]but-1-ynyl}phenyl)imidazolidine-2,4-dione

A solution of 3-(3-{4-[(6-bromohexyl)oxy]but-1-ynyl}phenyl)imidazolidine-2,4-dione and 20 3-(3-{4-[(6-iodohexyl)oxy]but-1-ynyl}phenyl)imidazolidine-2,4-dione (3:1, 23.98g) in acetonitrile (240ml) and diisopropylethylamine (20ml) was treated with (*1R*)-2-(benzylamino)-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol (18.22g) and the mixture was heated to 50°C for 5 days. The solvent was removed under reduced pressure, the residue was diluted with EtOAc (250ml) and washed with water. The 25 aqueous phase was re-extracted with EtOAc (75ml) and the combined organic solutions were washed with brine, dried (MgSO₄), and evaporated. The residue was purified by chromatography on flash silica gel eluting with dichloromethane-EtOAc (1:1) to give the *title compound* (17.25g) LCMS RT=2.80min

30 vi) 3-[3-(4-[(6-{(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy]butyl]phenyl]imidazolidine-2,4-dione

A solution of 3-(3-{4-[(6-{benzyl}[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]but-1-ynyl}phenyl)imidazolidine-2,4-dione (9.05g) in a

mixture of isopropanol-EtOAc (9:1, 200ml) was hydrogenated over Pearlman's catalyst (1.8g). After 2 days aqueous 2M HCl (10ml) was added and the mixture was hydrogenated for a further 2h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on Biotage eluting with dichloromethane-isopropanol-880 ammonia (34:7:1) to give *the title compound* (2.8g) LCMS RT=2.34min ES+ve 514 (MH)⁺.

Example 7: 3-[3-(4-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxybutyl]phenyl]imidazolidine-2,4-dione acetate

i) 6-(But-3-ynyloxy)hexanal

6-Bromohexylbut-3-ynyl ether (525mg) in DMSO (2ml) was added to a mixture of sodium bicarbonate (1g) in DMSO (8ml) at 150°C with vigorous stirring and nitrogen bubbling through the solution. The mixture was stirred for 20 min at 150 °C and then allowed to cool to room temperature, diluted with Et₂O and washed with water. The aqueous layer was extracted with Et₂O and the combined ether layers were washed with dilute hydrochloric acid, brine, dried (MgSO₄) and evaporated to dryness to give *the title compound* (325mg): IR 1726 cm⁻¹ MS(TSP+ve) m/z 186 (M+MH₄)⁺.

ii) (1R)-2-[(6-(But-3-ynyloxy)hexyl][(1S)-2-hydroxy-1-phenylethyl]amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol

A mixture of 6-(but-3-ynyloxy)hexanal (434mg) and (1R)-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-[(1S)-2-hydroxy-1-phenylethyl]amino]ethanol (WO0196278 A2) (710mg) in chloroform (10ml) was treated at 20°C with sodium triacetoxyborohydride (866mg) and stirred under nitrogen for 2 days. The mixture was diluted with EtOAc and aqueous sodium bicarbonate solution. The organic phase was separated and washed with sodium bicarbonate solution, brine, dried and purified on a silica Bond Elut cartridge (10g) eluting with dichloromethane, Et₂O and finally EtOAc to give *the title compound* (810mg): LCMS RT=2.69min, ES+ve m/z 496 (M+H)⁺.

iii) 3-(3-{4-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl][(1S)-2-hydroxy-1-phenylethyl]amino}hexyl)oxybut-1-ynyl]phenyl]imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 1ii
LCMS RT=2.82min, ES+ve 670 (MH)⁺.

iv) 3-[3-(4-{[(2R)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 6(vi)

LCMS RT=2.39min, ES+ve 514 (MH)⁺.

Example 8: 3-[3-(4-{[(2S)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione

acetate

i) 3-(3-{4-[(6-[(2S)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-

hydroxyethyl]amino}hexyl]oxy]but-1-ynyl}phenyl]imidazolidine-2,4-dione

15 was prepared using methods similar to those described in Example 5iv from

(1S)-2-amino-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol (*Tetrahedron:Asymmetry* 2001, 12, 2005).

ii) 3-(3-{4-[(6-[(2S)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-

hydroxyethyl]amino}hexyl]oxy]butyl}phenyl]imidazolidine-2,4-dione

20 was prepared using methods similar to those described in Example 5v.

iii) 3-[3-(4-{[(2S)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione

acetate

25 was prepared using methods similar to those described in Example 1xii.

Example 9: 3-[4-(4-{[(2R)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione

acetate

i) Ethyl N-[(4-iodophenyl)amino]carbonyl]glycinat

30 was prepared using method similar to those described in Example 5i.

LCMS RT=3.1min.

ii) 3-(4-Iodophenyl)imidazolidine-2,4-dione

was prepared using method similar to those described in Example 5ii.

5 LCMS RT=2.49min.

iii) 3-(4-{4-[6-Bromohexyl]oxy}but-1-ynyl)phenyl)imidazolidine-2,4-dione

was prepared using method similar to those described in Example 5iii.

LCMS RT=3.46min.

10 iv) 3-(4-{4-[6-{[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl]oxy}but-1-ynyl)phenyl)imidazolidine-2,4-dione

was prepared using method similar to those described in Example 5iv.

LCMS RT=2.58min.

15 v) 3-(4-{4-[6-{[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl]oxy}butyl)phenyl)imidazolidine-2,4-dione

was prepared using method similar to those described in Example 5v.

LCMS RT=2.55min.

20 vi) 3-[4-(4-{[6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino}hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione acetate

was prepared using method similar to those described in Example 1xii.

LCMS RT=2.34min, ES+ve 514(MH)⁺.

25

Example 10: 3-[2-(4-{[6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino}hexyl]oxy}butyl)phenyl]imidazolidine-2,4-dione acetate

30 i) Ethyl N-{{(2-iodophenyl)amino}carbonyl}glycinate

was prepared using method similar to those described in Example 5i.

LCMS RT=2.62min.

ii) 3-(2-Iodophenyl)imidazolidine-2,4-dione

A solution of ethyl *N*-{[(2-iodophenyl)amino]carbonyl}glycinate (6g) in MeOH was treated with aqueous NaOH (2M, 17.5ml) and stirred under nitrogen for 0.5h at 20 °C. The reaction mixture was quenched by adding aqueous 2M HCl (20ml) and water. The white solid obtained was collected by filtration and then was dissolved in dioxane (30ml) and treated with *p*-toluenesulfonic acid (750mg). The mixture was heated and stirred at 100°C for 16h. The solvent was removed under reduced pressure, the residue was diluted in EtOAc and washed with water, brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by chromatography on Biotage (40g) eluting with dichloromethane:EtOAc (95:5 to 85:15) to give *the title compound* (1.68g). LCMS RT=2.07min.

iii) 3-(2-{4-[(6-Bromohexyl)oxy]but-1-ynyl}phenyl)imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 5iii..

LCMS RT=3.29min.

iv) 3-(2-{4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy]but-1-ynyl}phenyl)imidazolidine-2,4-dione

was prepared using method similar to those described in Example 5iv.

LCMS RT=2.48min.

v) 3-(2-{4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy}butyl)phenyl)imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 5v.

LCMS RT=2.42min.

vi) 3-[2-(4-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]butyl]phenyl]imidazolidine-2,4-dione acetate

was prepared using method similar to those described in Example 1xii.

LCMS RT=2.08min, ES+ve 514(MH^+).

Example 11: 3-[3-(4-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy]butyl]benzyl]imidazolidine-2,4-dione acetate

5 i) Ethyl N-[(3-iodobenzyl)amino]carbonyl]glycinate

was prepared using methods similar to those described in Example 5i.

LCMS RT=2.71min.

ii) 3-(3-Iodobenzyl)imidazolidine-2,4-dione

10 A solution of ethyl N-[(3-iodobenzyl)amino]carbonyl]glycinate (7.6g) in MeOH (40ml) was treated with aqueous 2M NaOH (21.2ml) and stirred under nitrogen at 20°C. The mixture crushed out instantly and was quenched by adding aqueous 2M HCl (22ml). The residue was filtered to give *the title compound* (4.4g) LCMS=2.73min.

15 iii) 3-(3-{4-[(6-Bromohexyl)oxy]but-1-ynyl}benzyl)imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 5iii.

LCMS RT=3.35min.

iv) 3-(3-{4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-

20 hydroxyethyl]amino}hexyl)oxy]but-1-ynyl}benzyl)imidazolidine-2,4-dione

was prepared using method similar to those described in Example 5iv.

LCMS RT=2.52min.

v) 3-(3-{4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-

25 hydroxyethyl]amino}hexyl)oxy]butyl}benzyl)imidazolidine-2,4-dione

was prepared using method similar to those described in Example 5v.

LCMS RT=2.70min.

vi) 3-[3-(4-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-

30 (hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy]butyl}benzyl]imidazolidine-2,4-dione acetate

was prepared using method similar to those described in Example 1xii.

LCMS RT=2.44min, ES+ve 528(MH)⁺.

Example 12: 3-[3-(5-[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)pentyl]oxy]pentyl]phenyl]imidazolidine-2,4-dione acetate

5

i) 5-[(5-Bromopentyl)oxy]pent-1-yne

was prepared using methods similar to those described in Example 1i.

LCMS RT=3.62min.

10

ii) 5-Bromopentyl 5-(3-nitrophenyl)pent-4-ynyl ether

was prepared using methods similar to those described in Example 1ii. TLC Rf=0.18 (Et₂O-petroleum ether 1:19)

iii) 5-[(5-(3-Nitrophenyl)pent-4-ynyl)oxy]pentyl acetate

15

was prepared using methods similar to those described in Example 1iii. LCMS RT=3.69min

iv) 5-[(5-(3-Aminophenyl)pentyl)oxy]pentyl acetate

was prepared using methods similar to those described in Example 1iv. LCMS RT=3.12min

20

v) Ethyl N-((3-(5-[(5-(acetyloxy)pentyl)oxy]pentyl)phenyl)amino)carbonyl)glycinate

was prepared using methods similar to those described in Example 1v. LCMS

RT=3.45min

25

vi) 3-(3-{5-[(5-Hydroxypentyl)oxy]pentyl}phenyl)imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 1vi. LCMS

RT=2.77min

vii) 5-[(5-{3-[3-(2,5-Dioxoimidazolidin-1-yl)]phenyl}pentyl)oxy]pentyl methanesulfonate

30

was prepared using methods similar to those described in Example 1vii. LCMS

RT=3.05min

viii) 3-(3-{5-[(5-Bromopentyl)oxy]pentyl}phenyl)imidazolidine-2,4-dione

A solution of 5-[(5-{3-[3-(2,5-dioxoimidazolidin-1-yl)]phenyl}pentyl)oxy]pentyl methanesulfonate (1.72g) in acetonitrile (30ml) was treated with tetrabutylammonium bromide (2.6g) at 20°C. After two days more tetrabutylammonium bromide (1g) was added and the mixture was stirred for a further day. The solvent was removed under reduced pressure and the residue was purified by chromatography on a Biotage cartridge (40g) eluting with EtOAc-petroleum ether (1:2, 1:1) to give *the title compound* (754mg) LCMS RT=3.36min

5 ix) 3-(3-{5-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-

10 hydroxyethyl]amino}pentyl)oxy]pentyl]phenyl)imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 1xi LCMS
RT=2.48min

15 x) 3-[3-(5-[(2R)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl]amino)pentyl]oxy]pentyl]phenyl]imidazolidine-2,4-dione
acetate

was prepared using methods similar to those described in Example 1xii LCMS
RT=2.22min, ES+ve 514 (MH)⁺.

20 **Example 13:** 3-[3-(5-[(2R)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]pentyl]phenyl]imidazolidine-2,4-dione
acetate

i) 5-[(6-Bromohexyl)oxy]pent-1-yne

25 was prepared using methods similar to those described in Example 1i.

GCMS RT = 5.6min

ii) 3-(3-{5-[(6-Bromohexyl)oxy]pent-1-ynyl}phenyl)imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 5iii LCMS

30 RT=3.57min

iii) 3-(3-{5-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-

hydroxyethyl]amino}hexyl)oxy]pent-1-ynyl]phenyl)imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 5iv LCMS
RT=2.54min

iv) 3-(3-{5-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy}pentyl}phenyl)imidazolidine-2,4-dione

5

was prepared using methods similar to those described in Example 5v LCMS
RT=2.71min

v) 3-[3-(5-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy}pentyl}phenyl)imidazolidine-2,4-dione acetate

10

was prepared using methods similar to those described in Example 1xii LCMS
RT=2.47min, ES+ve 528 (MH)⁺.

15

Example 14: 3-[3-(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy}hexyl}phenyl)imidazolidine-2,4-dione acetate

20

i) 6-[(6-Bromoethyl)oxy]hex-1-yne

was prepared using methods similar to those described in Example 1i.

GCMS RT=5.99min

ii) 3-(3-Iodophenyl)imidazolidine-2,4-dione

was prepared using method similar to those described in Example 5ii.

25

LCMS RT=2.54min.

iii) 3-(3-{6-[(6-Bromoethyl)oxy]hex-1-ynyl}phenyl)imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 5iii.

LCMS RT=3.55min.

30

iv) 3-(3-{6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy}hex-1-ynyl}phenyl)imidazolidine-2,4-dione

was prepared using method similar to those described in Example 5iv.

LCMS RT=2.68min.

v) 3-(3-{[6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy}hexyl]phenyl)imidazolidine-2,4-dione

5 was prepared using method similar to those described in Example 5v.

LCMS RT=2.73min.

vi) 3-[3-(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy}hexyl]phenyl)imidazolidine-2,4-dione

10 acetate

was prepared using method similar to those described in Example 1xii.

LCMS RT=2.81min, ES+ve 582(MH)⁺.

Example 15: (5R)-5-[3-(4-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-

15 (hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy}butyl]benzyl]-5-methylimidazolidine-2,4-dione acetate

i) Benzyl (2S,4R)-4-(3-iodobenzyl)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate

20 A solution of benzyl (2S,4S)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate (*J. Org. Chem.* 2001, 66, 1903) (1.2g) and 3-iodobenzyl bromide (1.15g) in THF (8ml) was added dropwise to a solution of lithium hexamethyldisilazide in THF (1M, 4.1ml) diluted in THF (32ml) at -30°C. The mixture was stirred at this temperature and then allowed to warm to 20°C over 4h. Aqueous sodium bicarbonate solution was then added and the 25 mixture was extracted with Et₂O. The organic phase was separated and dried (MgSO₄), filtered and evaporated. The residue was purified by chromatography on a Biotage cartridge (40g) eluting with EtOAc-petroleum ether (1:9, 1:4) to give the *title compound* (1.48g) HPLC RT=9.33min.

30 ii) 3-Iodo- α -methyl-D-phenylalanine

A mixture of benzyl (2S,4R)-4-(3-iodobenzyl)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate (1.47g) and potassium trimethylsilanolate (1.2g) was suspended in THF (50ml) and heated to 75°C for 2.5h. MeOH (10ml) was added and the solvents were

removed under reduced pressure. The residue was dissolved in MeOH and applied to two 10g SCX-2 cartridges eluting with MeOH and then with 0.2 M ammonia in MeOH. The ammoniacal solutions were evaporated to dryness to give *the title compound* (910mg) LCMS RT=1.93min.

5 iii) Methyl 3-iodo- α -methyl-D-phenylalaninate

A solution of 3-iodo- α -methyl-D-phenylalanine (0.9g) in MeOH (50ml) was treated with thionyl chloride (3.5ml) and the mixture was heated to reflux for 3 days. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc and washed with aqueous sodium bicarbonate, brine, dried ($MgSO_4$) and evaporated to dryness to give *the title compound* (0.73g) LCMS RT=2.12min.

10

iv) Methyl N-(aminocarbonyl)-3-iodo- α -methyl-D-phenylalaninate

A mixture of methyl 3-iodo- α -methyl-D-phenylalaninate (0.73g) in acetic acid (3ml) and water (1ml) was treated with sodium cyanate (0.4g) and stirred for 2 days at 20°C. The solvents were removed under reduced pressure and the residue was diluted with EtOAc. The solution was washed with water, brine, dried ($MgSO_4$) and evaporated to give *the title compound* (0.82g) LCMS RT=2.74min.

15

v) (5R)-5-(3-Iodobenzyl)-5-methylimidazolidine-2,4-dione

20 A mixture of methyl *N*-(aminocarbonyl)-3-iodo- α -methyl-D-phenylalaninate (0.82g) and potassium carbonate (624mg) in dimethyl sulfoxide (5ml) was heated to 110°C for 3h and then allowed to cool to 20°C overnight. The mixture was diluted with EtOAc and washed with 2M HCl, brine, dried ($MgSO_4$) and evaporated to dryness to give *the title compound* (521mg) LCMS RT=2.61min

25

vi) (5R)-5-(3-{4-[6-Bromohexyl]oxy}but-1-ynyl)benzyl)-5-methylimidazolidine-2,4-dione

was prepared using methods similar to those described in Example 5iii LCMS

RT=3.36min

30

vii) (5R)-5-(3-{4-[{[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl]oxy}but-1-ynyl)benzyl)-5-methylimidazolidine-2,4-dione

was prepared using methods similar to those described in Example 5iv LCMS

RT=2.58min

viii) (5R)-5-[3-(4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy]butyl]benzyl]-5-methylimidazolidine-2,4-dione
was prepared using methods similar to those described in Example 5v LCMS

5 RT=2.69min

ix) (5R)-5-[3-(4-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]butyl]benzyl]-5-methylimidazolidine-2,4-dione acetate

10 was prepared using methods similar to those described in Example 1xii LCMS

RT=2.41min, ES+ve 542(MH)⁺.

Example 16: (5S)-5-[3-(4-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]butyl]benzyl]-5-methylimidazolidine-2,4-dione acetate

i) Benzyl (2R,4S)-4-(3-iodobenzyl)-4-methyl-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate

was prepared using methods similar to those described in Example 15i LCMS

20 RT=3.98min

ii) 3-Iodo- α -methyl-L-phenylalanine

was prepared using methods similar to those described in Example 15ii LCMS

RT=2.03min

25

iii) Methyl 3-iodo- α -methyl-L-phenylalaninate

was prepared using methods similar to those described in Example 15iii LCMS

RT=2.21min

30

iv) Methyl N-(aminocarbonyl)-3-iodo- α -methyl-L-phenylalaninate

was prepared using methods similar to those described in Example 15iv LCMS

RT=2.78min

v) (5S)-5-(3-Iodobenzyl)-5-methylimidazolidine-2,4-dione

was prepared using methods similar to those described in Example 15v LCMS

RT=2.69min

5 vi) (5S)-5-(3-{4-[(6-Bromohexyl)oxy]but-1-ynyl}benzyl)-5-methylimidazolidine-2,4-dione

was prepared using methods similar to those described in Example 5iii LCMS

RT=3.39min

10 vii) (5S)-5-(3-{4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]but-1-ynyl}benzyl)-5-methylimidazolidine-2,4-dione

was prepared using methods similar to those described in Example 5iv LCMS

RT=2.63min

15 viii) (5S)-5-(3-{4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}benzyl)-5-methylimidazolidine-2,4-dione

was prepared using methods similar to those described in Example 5v LCMS

RT=2.65min

20 ix) (5S)-5-[3-(4-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]butyl]benzyl]-5-methylimidazolidine-2,4-dione acetate

was prepared using methods similar to those described in Example 1xii LCMS

RT=2.37min, ES+ve 542(MH)⁺.

25 Example 17: 2-[3-[3-(4-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]butyl]phenyl]-2,4-dioxoimidazolidin-1-yl]acetamide acetate

i) 2-[3-(3-Iodophenyl)-2,4-dioxoimidazolidin-1-yl]acetamide

A solution of 3-(3-iodophenyl)imidazolidine-2,4-dione (1g) in DMF (20ml) was treated with sodium hydride (60% oil dispersion, 158mg) and 2-bromoacetamide (1.36g) at 20°C. After 2h the reaction mixture was treated with aqueous 2M HCl, extracted with EtOAc and dried (MgSO₄). The solvent was removed under reduced pressure and the

residue was purified by chromatography on Biotage (40g) eluting with EtOAc to give *the title* compound (638mg). LCMS RT=2.32min.

5 ii) 2-[3-(3-{4-[(6-Bromohexy)oxy]but-1-ynyl}phenyl)-2,4-dioxoimidazolidin-1-yl]acetamide

was prepared using methods similar to those described in Example 5iii.
LCMS RT=3.17min.

10 iii) 2-[3-(3-{4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]but-1-ynyl}phenyl)-2,4-dioxoimidazolidin-1-yl]acetamide

was prepared using methods similar to those described in Example 5iv.
LCMS RT=2.50min.

15 iv) 2-[3-(3-{4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}phenyl)-2,4-dioxoimidazolidin-1-yl]acetamide

was prepared using methods similar to those described in Example 5v.
LCMS RT=2.59min.

20 v) 2-[3-(4-[(6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy]butyl]phenyl]-2,4-dioxoimidazolidin-1-yl]acetamide acetate

was prepared using method similar to those described in Example 1xii.
LCMS RT=2.23min, ES+ve 571(MH)⁺.

25 **Example 18:** 5-[4-(4-[(6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy]butyl]benzyl]imidazolidine-2,4-dione compound with formic acid (1:1)

30 i) Methyl N-(aminocarbonyl)-4-iodo-L-phenylalaninate

was prepared using methods similar to those described in Example 15iv LCMS
RT=2.78min

ii) 5-(4-Iodobenzyl)imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 15v LCMS

RT=2.54min

5 iii) 5-[4-[4-({6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)but-1-ynyl]benzyl]imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 3viii

LCMS RT=3.22min

10 iv) 5-[4-[4-({6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]benzyl]imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 3ix

LCMS RT=3.41min

15 v) 5-[4-(4-{{6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl}amino)hexyl}oxy}butyl]benzyl]imidazolidine-2,4-dione
compound with formic acid (1:1)

was prepared using methods similar to those described in Example 3x

20 **Example 19:** 1-[3-(4-{{6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl}amino)hexyl}oxy}butyl]phenyl]-1,3-dihydro-2H-imidazol-2-one

25 i) N-(2,2-Dimethoxyethyl)-N-(3-iodophenyl)urea

A suspension of 3-iodophenylisocyanate (1.1g) in DCM (10ml) was treated with
aminoacetaldehyde dimethyl acetal (0.49ml) and stirred under nitrogen at 20°C for 24h.
The reaction mixture was quenched by adding MeOH. The solvents were removed
under reduced pressure to give *the title compound* (1.35g) LCMS RT=2.92min.

30 ii) 1-(3-Iodophenyl)-1,3-dihydro-2H-imidazol-2-one

N-(2,2-Dimethoxyethyl)-N-(3-iodophenyl)urea (618mg) was dissolved in acetic acid
(10ml) and water (1ml) and the mixture was stirred at 20°C for 17h and then heated to
100°C for 0.5h. The solvent was removed under reduced pressure and the residue was
dissolved in ethyl acetate. The solution was washed with NaHCO₃ solution, dried and

purified by chromatography on 10g silica Bond Elut cartridge eluting with EtOAc-petroleum ether (1:7 to 1:1) to give *the title compound* (130mg) LCMS RT=2.66min.

- 5 iii) 1-[3-(4-[(2R)-2-Hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]-1,3-dihydro-2H-imidazol-2-
- one
- may be prepared using for example the methods described in Example 5ii to 5vi.
LCMS RT=2.28min, ES+ve 498 (MH)⁺.

10

Example 20: 3-[3-(4-[(2R)-2-Hydroxy-2-[4-hydroxy-3-
(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)phenyl]-5,5-dimethylimidazolidine-

2,4-dione acetate

15

i) 3-(3-Iodophenyl)-5,5-dimethylimidazolidine-2,4-dione

BOC- α -methylalanine (1.01g) and diisopropylethylamine (1.74ml) in dichloromethane (2ml) was treated with tetramethylfluoroformamidinium hexafluorophosphate (1.32g) and the mixture was stirred for 18h. 3-Iodoaniline (1.09g) in dichloromethane (2ml) was added, followed by diisopropylethylamine (1ml). The mixture was stirred for 84h and then the solvents were removed under reduced pressure. The residue was partitioned between EtOAc and 2M HCl. The organic solution was washed with 2M HCl, sodium bicarbonate solution, brine and dried ($MgSO_4$). The filtrate was concentrated and then triturated in dichloromethane-cyclohexane (1:1, 20ml) to give a solid (740mg). The solution was purified by chromatography on two 10g silica Bond Elut cartridges eluting with dichloromethane to give additional solid (633mg). LCMS RT=3.41min. The solid (735mg) was dissolved in DMF (3ml) and then treated with sodium hydride (60% oil dispersion, 109mg). The mixture was stirred overnight at room temperature and then heated to 75°C for 3h. The solvent was removed under reduced pressure and treated with 4M HCl in dioxane. The resulting solution was heated for 2h at 75°C, concentrated, and the residue was triturated in Et_2O to give *the title compound* (487mg). LCMS RT=2.79min

ii) 3-(3-{4-[6-Bromohexyl]oxy}but-1-ynyl}phenyl)-5,5-dimethylimidazolidine-2,4-dione

was prepared using methods similar to those described in Example 5iii.LCMS

RT=3.51min

- 5 iii) 3-(3-{4-[6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl]oxy}but-1-ynyl}phenyl)-5,5-dimethylimidazolidine-2,4-dione
was prepared using methods similar to those described in Example 5iv.LCMS
RT=2.72min

- 10 iv) 3-(3-{4-[6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl]oxy}butyl}phenyl)-5,5-dimethylimidazolidine-2,4-dione
was prepared using methods similar to those described in Example 5v.LCMS
RT=2.60min

- 15 v) 3-[3-(4-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyl]oxy]butyl}phenyl]-5,5-dimethylimidazolidine-2,4-dione acetate
was prepared using methods similar to those described in Example 1xii.LCMS
RT=2.47min, ES+ve 542 (MH)⁺.

- 20 **Example 21:** 3-[3-(3-{[7-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)heptyl]oxy}propyl}phenyl]-1-(methylsulfonyl)imidazolidine-2,4-dione acetate

- 25 i) 7-[3-{3-[3-(methylsulfonyl)-2,5-dioxoimidazolidin-1-yl]phenyl}propyl]oxy]heptyl methanesulfonate
was prepared using methods similar to those described in Example 1vii.LCMS
RT=2.80min

- 30 ii) 3-(3-{3-[7-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}heptyl]oxy}propyl}phenyl)-1-(methylsulfonyl)imidazolidine-2,4-dione
was prepared using methods similar to those described in Example 1xi. LCMS
RT=2.85min

iii) 3-[3-(3-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)heptyloxy]propyl]phenyl]-1-(methylsulfonyl)imidazolidine-2,4-dione acetate

5 was prepared using methods similar to those described in Example 1xii. LCMS RT=2.54min, ES+ve 592 (MH)⁺.

Example 22: 1-[3-(3-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy]propyl]phenyl]-imidazolidine-2,4-dione acetate

i) 1-[3-[3-((6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)prop-1-ynyl]phenyl]-imidazolidine-2,4-dione

10 was prepared using methods similar to those described in Example 4ii. LCMS
15 RT=3.43min

ii) 1-[3-[3-((6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy)propyl]phenyl]-imidazolidine-2,4-dione

20 was prepared using methods similar to those described in Example 3ix. LCMS
RT=3.42min

iii) 1-(3-[3-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino]hexyl]oxy]propyl]phenyl]-imidazolidine-2,4-dione

25 was prepared using methods similar to those described in Example 3x. LCMS RT=2.60min

iv) 1-[3-(3-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy]propyl]phenyl]-imidazolidine-2,4-dione acetate

30 was prepared using methods similar to those described in Example 1xii. LCMS RT=2.34min, ES+ve 500 (MH)⁺

Example 23: N-[1-[3-(4-[(6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl]benzyl]-2,5-dioxoimidazolidin-4-yl]urea acetate

5 i) N-[1-(3-Iodobenzyl)-2,5-dioxoimidazolidin-4-yl]urea

Allantoin (1.58g) was stirred with *meta*-iodobenzyl bromide (2.97g) in DMF (25ml) at 21° under nitrogen and sodium hydride (60% oil dispersion; 0.40g) was added over 5min. After 2h the solution was partitioned between EtOAc and water and hydrochloric acid was added to give pH 3. The separated aqueous layer was extracted with more EtOAc and the combined organic layers were washed with water and brine twice. After drying (MgSO₄), the solution was concentrated to 20ml. After 1h the solid was collected by filtration and washed with EtOAc. The residue was boiled with EtOAc (50ml) and the slurry was allowed to cool. The solid was collected by filtration, washed with ethyl acetate and dried to give the *title compound* (0.507g). LCMS RT=2.44min

15

ii) N-[1-(3-[4-[(6-Bromohexyl)oxy]but-1-ynyl]benzyl)-2,5-dioxoimidazolidin-4-yl]urea
was prepared using methods similar to those described in Example 5iii. LCMS RT=3.29min

20

iii) N-[1-(3-[4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy]but-1-ynyl]benzyl)-2,5-dioxoimidazolidin-4-yl]urea
was prepared using methods similar to those described in Example 5iv. LCMS RT=2.57min

25

iv) N-[1-(3-[4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino)hexyl]oxy]butyl]benzyl)-2,5-dioxoimidazolidin-4-yl]urea
was prepared using methods similar to those described in Example 5v. LCMS RT=2.61min

30

v) N-[1-[3-(4-[(6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl]benzyl]-2,5-dioxoimidazolidin-4-yl]urea acetate

was prepared using methods similar to those described in Example 1xii. LCMS
RT=2.36min, ES+ve 586 (MH)⁺

Example 24: 3-Benzyl-1-[3-(4-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-

**(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl]phenyl]imidazolidine-2,4-dione
acetate**

i) 3-Benzyl-1-(3-iodophenyl)imidazolidine-2,4-dione

10 1-(3-Iodophenyl)imidazolidine-2,4-dione (0.5g) was taken up in dry DMF (10ml) and treated with sodium hydride (60% oil dispersion, 73mg) and stirred for 20 min under nitrogen. Benzyl bromide (0.295ml) was added and stirring continued for 3 h. 2M HCl (100ml) was added and the mixture extracted with EtOAc. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate (50ml), brine (50ml) and dried (MgSO_4). This was recrystallised from MeOH to give *the title compound* (0.255g).

15 LCMS RT 3.53min.

ii) 3-Benzyl-1-(3-{4-[(6-bromohexyl)oxy]but-1-ynyl}phenyl)imidazolidine-2,4-dione

20 was prepared using methods similar to those described in Example 5iii). LCMS
RT=3.99min

iii) 3-Benzyl-1-(3-{4-[(6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-

hydroxyethyl]amino}hexyl)oxy]but-1-ynyl}phenyl)imidazolidine-2,4-dione

25 was prepared using methods similar to those described in Example 5iv). LCMS
RT=3.02min

iv) 3-Benzyl-1-(3-{4-[(6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-

hydroxyethyl]amino}hexyl)oxy]butyl]phenyl]imidazolidine-2,4-dione

30 was prepared using methods similar to those described in Example 5v). LCMS
RT=3.08min

v) 3-Benzyl-1-[3-(4-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-

**(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl]phenyl]imidazolidine-2,4-dione
acetate**

was prepared using methods similar to those described in Example 1xii). LCMS RT=2.81min, ES+ve 604 (MH)⁺.

Example 25: 1-[3-(4-{[(2R)-2-Hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl)phenyl]-3-methylimidazolidine-2,4-dione acetate

i) 1-(3-Iodophenyl)-3-methylimidazolidine-2,4-dione

10 1-(3-Iodophenyl)imidazolidine-2,4-dione (0.588g) was suspended in water (13ml) and treated with potassium hydroxide (0.37g). The reaction was placed in a warming bath (45°C) and treated with dimethyl sulfate (0.784ml). After stirring for 4 h the reaction mixture was chilled and filtered. The cake was washed with water and dried to give *the title compound* (0.381g). LCMS RT=2.94min.

15 **ii) 1-(3-{4-[6-Bromohexyl]oxy]but-1-ynyl}phenyl)-3-methylimidazolidine-2,4-dione**
was prepared using methods similar to those described in Example 5iii). LCMS RT=3.64min.

20 **iii) 1-(3-{4-[6-{[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl}amino}hexyl]oxy]but-1-ynyl}phenyl)-3-methylimidazolidine-2,4-dione**
was prepared using methods similar to those described in Example 5iv). LCMS RT=2.79min.

25 **iv) 1-(3-{4-[6-{[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl}amino}hexyl]oxy}butyl)phenyl)-3-methylimidazolidine-2,4-dione**
was prepared using methods similar to those described in Example 5v). LCMS RT=2.76min.

30 **v) 1-[3-(4-{[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl)phenyl]-3-methylimidazolidine-2,4-dione acetate**
was prepared using methods similar to those described in Example 1xii). LCMS RT=2.48min, ES+ve 527 (MH)⁺.

Example 26: Ethyl [3-[3-(4-[(6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy]butyl]phenyl]-2,5-dioxoimidazolidin-1-yl]acetate acetate

5

i) Ethyl [3-(3-iodophenyl)-2,5-dioxoimidazolidin-1-yl]acetate

1-(3-Iodophenyl)imidazolidine-2,4-dione (0.5g) was dissolved in dry DMF (10ml) and treated with sodium hydride (60% oil dispersion, 73mg) and stirred under nitrogen. After 20 min ethyl chloroacetate (0.255ml) was added. After 3 h 2M HCl (100ml) was added and the mixture extracted with EtOAc. The combined extracts were dried (MgSO_4) and evaporated under reduced pressure. Trituration with di-*tert*-butyl ether (2x10ml) gave the title compound (0.571g). LCMS RT=3.21min.

10

ii) Ethyl [3-(3-{4-[(6-bromohexyl)oxy]but-1-ynyl}phenyl)-2,5-dioxoimidazolidin-1-yl]acetate

15

was prepared using methods similar to those described in Example 5iii). LCMS RT=3.79min.

20

iii) Ethyl [3-(3-{4-[(6-((2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl)amino)hexyl)oxy]but-1-ynyl}phenyl)-2,5-dioxoimidazolidin-1-yl]acetate

was prepared using methods similar to those described in Example 5iv). LCMS RT=2.85min.

25

iv) Ethyl [3-(3-{4-[(6-((2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-

hydroxyethyl)amino)hexyl)oxy]butyl]phenyl)-2,5-dioxoimidazolidin-1-yl]acetate

was prepared using methods similar to those described in Example 5v). LCMS RT=2.93min.

30

v) Ethyl {3-[3-(4-[(6-((2R)-2-hydroxy-2-[4-hydroxy-3-

(hydroxymethyl)phenyl]ethyl)amino)hexyl]oxy]butyl]phenyl]-2,5-dioxoimidazolidin-1-yl]acetate acetate

was prepared using methods similar to those described in Example 1xii). LCMS

RT=2.65min, ES+ve 600 (MH^+).

Example 27: 2-[3-[3-(4-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino]hexyl]oxy]butyl]phenyl]-2,5-dioxoimidazolidin-1-yl}acetamide acetate

5

i) 2-[3-(3-Iodophenyl)-2,5-dioxoimidazolidin-1-yl]acetamide

1-(3-Iodophenyl)imidazolidine-2,4-dione (0.302g) was taken up in dry DMF (15ml) and treated with bromoacetamide (0.399g) and then with sodium hydride (60% oil dispersion, 48mg). After 3 h pH 6.4 phosphate buffer (50ml) was added and the reaction mixture extracted with EtOAc (3x25ml), dried (MgSO_4) and evaporated under reduced pressure. The residue was purified by Flash chromatography (Merck 9385, EtOAc then 9:1 EtOAc:MeOH) to give *the title compound* (0.279g). LCMS RT=2.62min.

10

ii) 2-[3-(3-[4-[(6-Bromohexyl)oxy]but-1-ynyl}phenyl)-2,5-dioxoimidazolidin-1-yl]acetamide

15

was prepared using methods similar to those described in Example 5iii). LCMS RT=3.27min.

20

iii) 2-[3-(3-[4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino]hexyl)oxy]but-1-ynyl}phenyl)-2,5-dioxoimidazolidin-1-yl]acetamide
was prepared using methods similar to those described in Example 5iv). LCMS RT=2.47min.

25

iv) 2-[3-(3-[4-[(6-[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino]hexyl)oxy]butyl]phenyl]-2,5-dioxoimidazolidin-1-yl]acetamide
was prepared using methods similar to those described in Example 5v). LCMS RT=2.56min.

30

v) 2-[3-[3-(4-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino]hexyl]oxy]butyl]phenyl]-2,5-dioxoimidazolidin-1-yl}acetamide acetate

was prepared using methods similar to those described in Example 1xii). LCMS RT=2.31min, ES+ve 571 (MH^+).

Example 28: 1-[3-(4-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino)hexyloxy]butyl]benzyl]imidazolidine-2,4-dione acetate

5 i) Ethyl N-(3-iodobenzyl)glycinate

3-iodobenzylamine hydrochloride (1.0g) and diisopropylethylamine (1.29ml) were taken up in dry dimethylsulfoxide (60ml) and treated with ethyl bromoacetate and stirred under nitrogen for 2 h. 2M HCl (1.85ml) and water (250ml) were added. This was extracted with EtOAc, the aqueous phase was taken to pH 8 and extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography (Biotage, 40g) eluting with EtOAc-cyclohexane-diisopropylethylamine (10:89:1 then 20:79:1) to give *the title compound* (0.571g) LCMS RT 2.02 min.

15 ii) 1-(3-Iodobenzyl)imidazolidine-2,4-dione

Ethyl *N*-(3-iodobenzyl)glycinate (0.567g) was treated with 1M HCl (3.9ml) and sodium cyanate (0.345g) and then refluxed for 30 min. Concentrated HCl (4.5ml) was added and the reaction mixture refluxed again for 30 min. The reaction mixture was evaporated under reduced pressure and then triturated with EtOAc (3 x 20ml). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give *the title compound* (0.543g). LCMS RT 2.63min.

25 iii) 1-[3-[4-[(6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy]but-1-ynyl]benzyl]imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 3viii). LCMS RT=3.42min.

30 iv) 1-[3-[4-[(6-[(5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl]oxy]butyl]benzyl]imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 3ix). LCMS RT=3.4min.

v) 1-(3-{4-[{(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl]oxy}butyl}benzyl)imidazolidine-2,4-dione

was prepared using methods similar to those described in example 3x). LCMS
RT=2.6min.

5

vi) 1-[3-(4-[6-{(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl}benzyl)imidazolidine-2,4-dione acetate

was prepared using methods similar to those described in example 1xii). LCMS
10 RT=2.42min, ES+ve 528 (MH)⁺.

Example 29: 1-Benzyl-3-[3-(4-[6-{(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl}phenyl)imidazolidine-2,4-dione acetate

15

i) 1-Benzyl-3-(3-iodophenyl)imidazolidine-2,4-dione

A solution of 3-(3-iodophenyl)imidazolidine-2,4-dione (1.7g) in DMF (20ml) was treated with sodium hydride (60% oil dispersion, 280mg) and benzylchloride (1.93ml) at 20 °C. After 2h the reaction mixture was treated with aqueous 2M HCl, extracted with EtOAc and dried (MgSO₄). The solvent was removed under reduced pressure and the residue was purified by chromatography on Biotage (40g) eluting with petroleum ether-EtOAc (9:1 to 3:2) to give *the title* compound (1.38g). LCMS RT=3.27min.

25 ii) 3-Benzyl-1-(3-{4-[6-bromohexyl]oxy}but-1-ynyl)phenyl)imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 5iii.
LCMS RT=3.90min.

iii) 1-Benzyl-3-(3-{4-[6-{(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl]oxy}but-1-ynyl)phenyl)imidazolidine-2,4-dione

30 was prepared using methods similar to those described in Example 5iv.
LCMS RT=2.92min.

iv) 3-Benzyl-1-(3-[4-[(6-[(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl]oxy]butyl}phenyl)imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 5v.

LCMS RT=2.72min.

5

v) 1-Benzyl-3-[3-(4-[(6-[(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino}hexyl]oxy]butyl}phenyl]imidazolidine-2,4-dione acetate

was prepared using methods similar to those described in Example 1xii.

10 LCMS RT=2.67min, ES+ve 604(MH)⁺.

Example 30: 3-[3-(4-[(6-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl]amino}hexyl]oxy]butyl}phenyl]-1-(methylsulfonyl)imidazolidine-2,4-dione acetate

15

i) 3-(3-Iodophenyl)-1-(methylsulfonyl)imidazolidine-2,4-dione

A solution of 3-(3-iodophenyl)imidazolidine-2,4-dione (950mg) and *N,N*-diisopropylethylamine (1.1ml) in DCM (20ml) was treated with methanesulfonyl chloride (0.453ml) at 20 °C. After 2h the reaction mixture was diluted with DCM and washed with aqueous 2M HCl (3x20ml) and NaHCO₃ and dried (MgSO₄). The solvent was removed under reduced pressure to give *the title compound* (1.15g). LCMS RT=2.91min.

20

ii) 3-(3-[4-[(6-Bromohexyl)oxy]but-1-ynyl}phenyl)-1-(methylsulfonyl)imidazolidine-2,4-dione

25

was prepared using methods similar to those described in Example 5iii.

LCMS RT=3.60min.

30

iii) 3-(3-[4-[(6-{Benzyl}(2R)-2-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl]oxy]but-1-ynyl}phenyl)-1-(methylsulfonyl)imidazolidine-2,4-dione

was prepared using methods similar to those described in Example 6i.

LCMS RT=2.94min.

iv) 3-(3-{4-[{6-[{(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl}amino}hexyl]oxy}butyl}phenyl)-1-(methylsulfonyl)imidazolidine-2,4-dione
was prepared using methods similar to those described in Example 6ii.
LCMS RT=2.72min.

5

v) 3-[3-(4-[{6-{[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl)phenyl]-1-(methylsulfonyl)imidazolidine-2,4-dione acetate

was prepared using methods similar to those described in Example 1xii.
10 LCMS RT=2.48min, ES+ve 592(MH)⁺.

Example 31: 4-[3-(4-[{6-{[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl)phenyl]-1,2,4-triazolidine-3,5-dione acetate

15

i) Ethyl 2-[(3-iodophenyl)amino]carbonyl]hydrazinecarboxylate

A solution of ethyl carbazole (1.25g) in dichloromethane (20ml) was treated with 3-iodophenylisocyanate (1.7g) at 0°C. The reaction mixture was allowed to warm to 20°C and stirred for 2h. Ethanol (2ml) was added and the mixture was stirred for 0.5h. The solvents were removed under reduced pressure and the residue was triturated in diethyl ether. The white solid was collected by filtration to give *the title compound* (2.4g).
20 LCMS RT=2.81min

ii) Ethyl 2-[(3-[4-{[6-{[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy]but-1-ynyl}phenyl}amino]carbonyl]hydrazinecarboxylate

Was prepared using methods similar to those described in Example 3viii
25 LCMS RT=3.46min

iii) Ethyl 2-[(3-[4-{[6-{[(5R)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy]butyl}phenyl}amino]carbonyl]hydrazinecarboxylate

Was prepared using methods similar to those described in Example 3ix
30 LCMS RT=3.50min

iv) 4-(3-[{4-[6-{[(2R)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl]oxy}butyl]phenyl)-1,2,4-triazolidine-3,5-dione

Was prepared using methods similar to those described in Example 3x

LCMS RT=2.42min

5

v) 4-[3-(4-[{6-{[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl]phenyl]-1,2,4-triazolidine-3,5-dione acetate

Was prepared using methods similar to those described in Example 1xii

10 LCMS RT=2min, ES+ve 515 (MH)⁺

BIOLOGICAL ACTIVITY

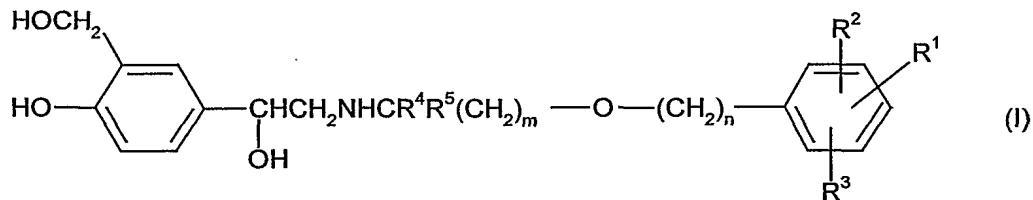
15 The potencies of the aforementioned compounds were determined using frog melanophores transfected with the human beta 2 adrenoreceptor. The cells were incubated with melatonin to induce pigment aggregation. Pigment dispersal was induced by compounds acting on the human beta 2 adrenoreceptor. The beta 2 agonist activity of test compounds was assessed by their ability to induce a change in light transmittance across a melanophore monolayer (a consequence of pigment dispersal).
20 At the human beta 2 adrenoreceptor, compounds of examples 1-31 had IC₅₀ values below 1 μM.

25 Potency at other beta adrenoreceptor subtypes was determined using chinese hamster ovary cells transfected with either the human beta 1 adrenoreceptor or the human beta 3 adrenoreceptor. Agonist activity was assessed by measuring changes in intracellular cyclic AMP.

30 The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims

1. A compound of formula (I)



5

or a salt, solvate or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8;

10 n is an integer of from 3 to 11;

with the proviso that m + n is 5 to 19;

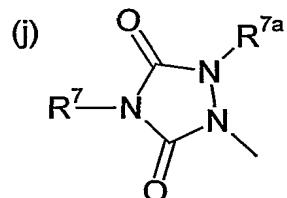
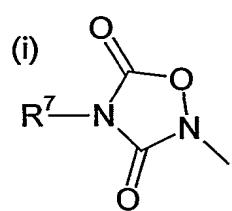
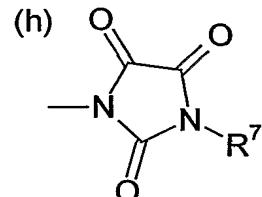
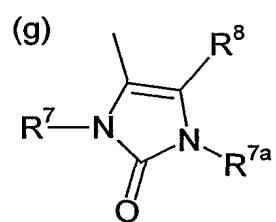
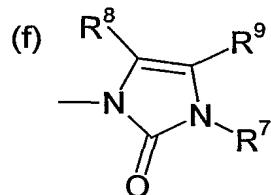
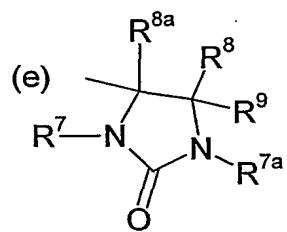
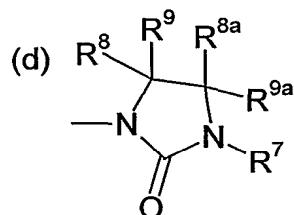
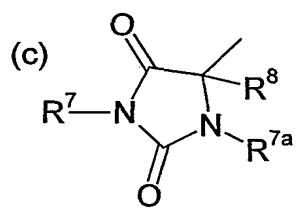
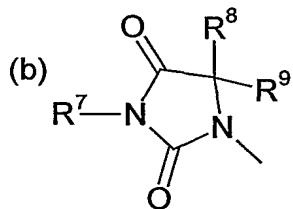
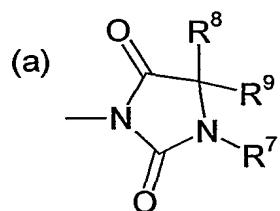
R¹ is -X-R⁶; wherein

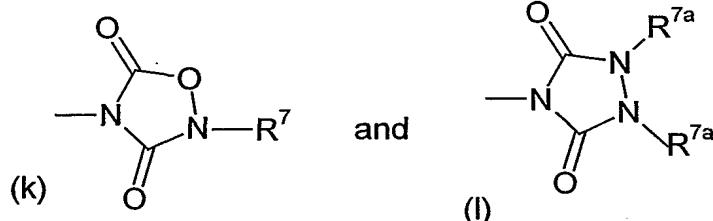
15 X is selected from -(CH₂)_p- and C₂₋₆alkenylene;

R⁶ is selected from

20

90





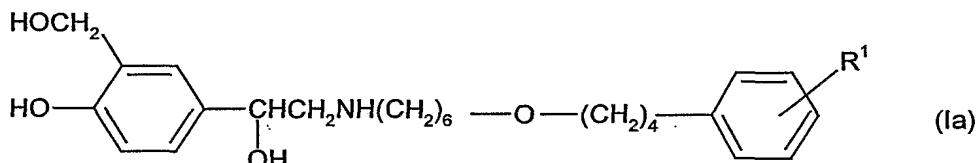
- 5 R^7 and R^{7a} are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, $C(O)R^{7b}$, $C(O)NHR^{7b}$, phenyl, naphthyl, hetaryl, and phenyl(C_{1-4} alkyl)-, and R^7 and R^{7a} are optionally substituted by 1 or 2 groups independently selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, $-NHC(O)(C_{1-6}$ alkyl), $-SO_2(C_{1-6}$ alkyl), $-SO_2$ (phenyl), $-CO_2H$, and $-CO_2(C_{1-4}$ alkyl);
- 10 R^{7b} is selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, naphthyl, hetaryl, and phenyl(C_{1-4} alkyl), and R^{7b} is optionally substituted by 1 or 2 groups independently selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, $-NHC(O)(C_{1-6}$ alkyl), $-SO_2(C_{1-6}$ alkyl), $-SO_2$ (phenyl), $-CO_2H$, and $-CO_2(C_{1-4}$ alkyl);
- 15 R^8 , R^{8a} , R^9 and R^{9a} are independently selected from hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, phenyl, naphthyl, hetaryl, phenyl(C_{1-4} alkyl)-, $-NR^{10a}SO_2R^{10}$, $-NR^{10a}C(O)NR^{10}R^{11}$, $-SO_2NR^{10}R^{11}$, and C_{1-6} alkyl substituted by $-CO_2R^{10}$ or $-C(O)NR^{10}R^{11}$;
- 20 R^{10} , R^{10a} and R^{11} are independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and phenyl (C_{1-4} alkyl)-;
- 25 p is an integer from 0 to 6;
- 25 R^2 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, halo, and C_{1-6} haloalkyl; R^3 is selected from hydrogen, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, phenyl, halo, C_{1-6} haloalkyl, $-NR^7CONR^7R^{7a}$, and $-SO_2NR^aR^b$;

wherein R^a and R^b are independently selected from hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, phenyl, and phenyl (C₁₋₄alkyl), or R^a and R^b, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring;

5 and R^a and R^b are each optionally substituted by one or two groups selected from halo, C₁₋₆alkyl, and C₁₋₆haloalkyl; and

R⁴ and R⁵ are independently selected from hydrogen and C₁₋₄alkyl with the proviso
10 that the total number of carbon atoms in R⁴ and R⁵ is not more than 4.

2. A compound of formula (Ia)

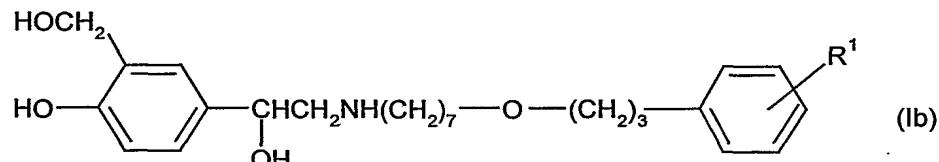


15

wherein

R¹ is as defined in claim 1 for formula (I),
20 or a salt, solvate, or physiologically functional derivative thereof.

3. A compound of formula (Ib)



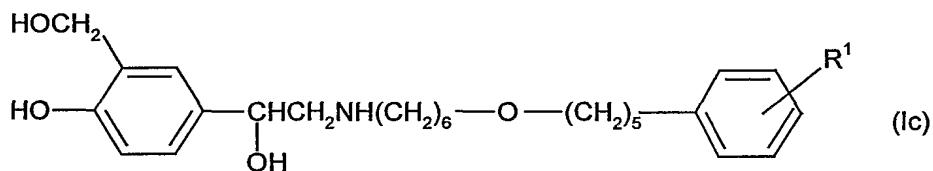
25

wherein R¹ is as defined in claim 1 for formula (I),

or a salt, solvate, or physiologically functional derivative thereof.

4. A compound of formula (Ic):

5



wherein R¹ is as defined above for formula (I),
or a salt, solvate, or physiologically functional derivative thereof.

10

5. A compound according to claim 1 or claim 2 selected from:

3-[3-(4-{{[6-((2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)}-amino}hexyl]oxy}butyl]phenyl]imidazolidine-2,4-dione;

15 3-[3-(4-{{[6-((2S)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)}-amino}hexyl]oxy}butyl]phenyl]imidazolidine-2,4-dione;

3-[3-(4-{{[6-((2R/S)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl)}-amino}hexyl]oxy}butyl]phenyl]imidazolidine-2,4-dione;

20 2-{3-[3-(4-{{[6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl]phenyl]-2,5-dioxoimidazolidin-1-yl}acetamide; and

N-{1-[3-(4-{{[6-((2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino}hexyl]oxy}butyl]benzyl]-2,5-dioxoimidazolidin-4-yl}urea;

25

or a salt, solvate or physiologically functional derivative thereof.

6. A compound according to claim 1 or claim 4 selected from:

3-[3-(5-[(2R)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}pentyl)phenyl]imidazolidine-2,4-dione

or a salt, solvate or physiologically acceptable derivative thereof.

5

7. A compound according to any of claims 1 to 6 wherein R⁶ is selected from one of the moieties (a) – (j) as defined in claim 1.

10 8. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β₂-adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I), (Ia), (Ib) or (Ic) according to any of claims 1 to 7, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

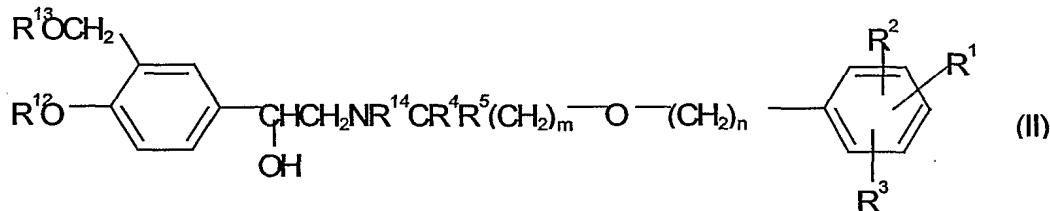
15 9. A compound of formula (I), (Ia), (Ib) or (Ic) according to any of claims 1 to 7, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy.

20 10. A pharmaceutical formulation comprising a compound of formula (I), (Ia), (Ib) or (Ic) according to any of claims 1 to 7, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

25 11. The use of a compound of formula (I), (Ia), (Ib) or (Ic) according to any of claims 1 to 7, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β₂-adrenoreceptor agonist is indicated.

30 12. A process for the preparation of a compound of formula (I), (Ia), (Ib) or (Ic) according to any of claims 1 to 7, or a salt, solvate, or physiologically functional derivative thereof, which comprises:

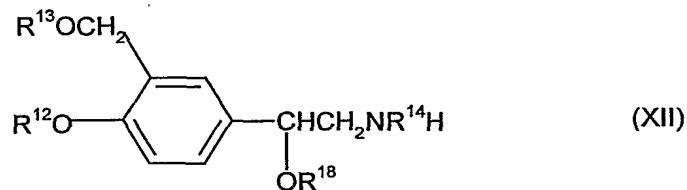
(a) deprotection of a protected intermediate, for example of formula (II):



or a salt or solvate thereof, wherein R^1 , R^2 , R^3 , R^4 , R^5 , m , and n are as defined for the compound of formula (I) or (Ia), and R^{12} , R^{13} , and R^{14} are each independently either hydrogen or a protecting group provided that at least one of R^{12} , R^{13} , and R^{14} is a protecting group; or

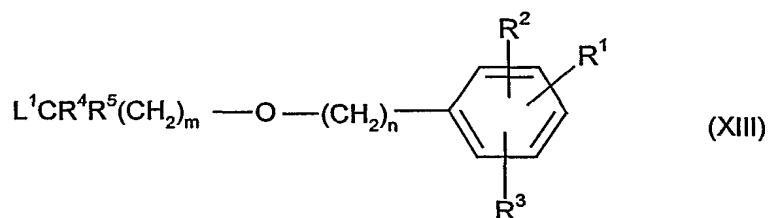
(b) alkylation of an amine of formula (XII)

10



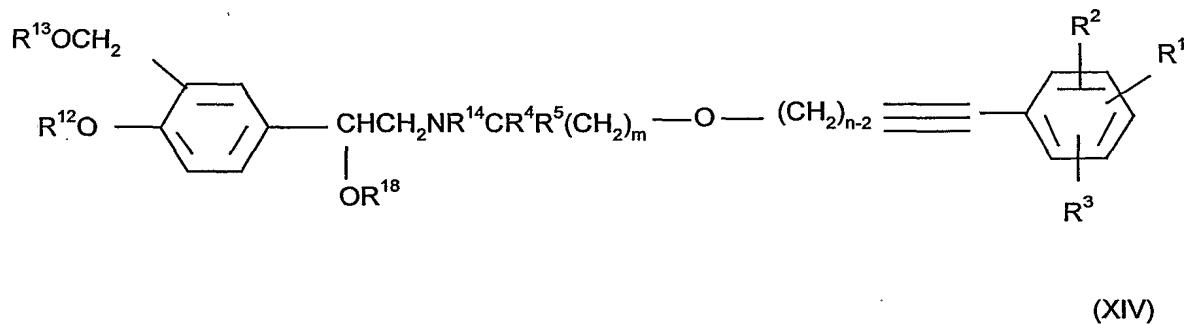
wherein R^{12} , R^{13} , R^{14} and R^{18} are each independently either hydrogen or a protecting group,

15 with a compound of formula (XIII):



20 wherein R^1 , R^2 , R^3 , R^4 , R^5 , m , and n are as defined for the compound of formula (I) or (Ia) and L^1 is a leaving group;

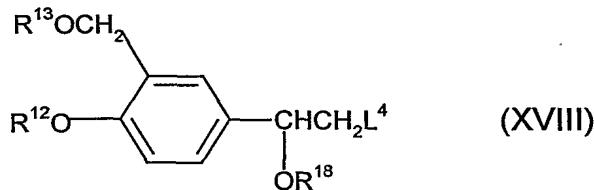
(c) reduction of a compound of formula (XIV):



wherein R^1 , R^2 , R^3 , R^4 , R^5 , m and n are as defined for formula (I) and R^{12} , R^{13} , R^{14} and R^{18} each independently represent a hydrogen atom or a protecting group as defined above;

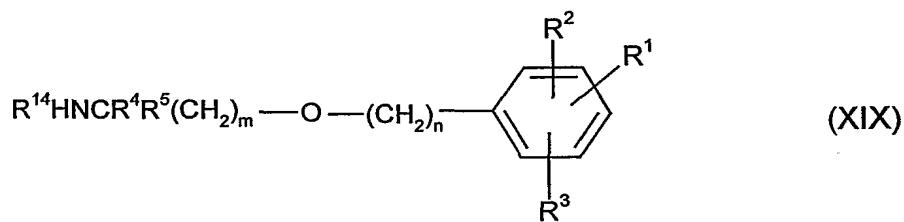
5

(d) reacting a compound of formula (XVIII):



10

wherein R^{12} , R^{13} and R^{18} are as hereinbefore defined and L^4 is a leaving group, with an amine of formula (IX):

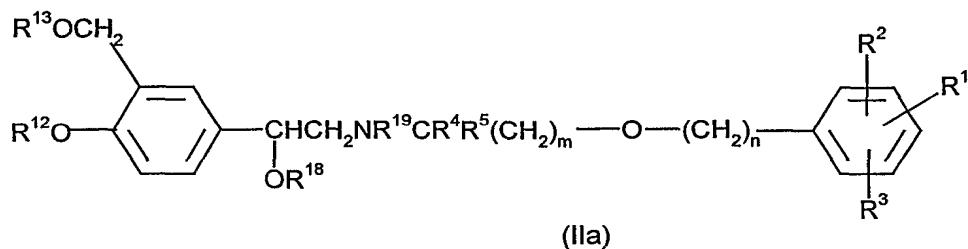


15

or

(e) removal of a chiral auxiliary from a compound of formula (IIa):

5



10 wherein R¹, R², R³, R⁴, R⁵, m and n are as defined for formula (I) and R¹², R¹³, R¹⁴ and R¹⁸ each independently represent a hydrogen atom or a protecting group as defined above and R¹⁹ represents a chiral auxiliary;

followed by the following steps in any order:

- 15 (i) optional removal of any protecting groups;
 (ii) optional separation of an enantiomer from a mixture of enantiomers;
 (iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

20 13. A compound for formula (II), (III) or (XIV) as defined hereinabove.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/02317

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D233/74 A61K31/395 A61P11/08 C07D233/70 C07D233/84
C07D249/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELD OF SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 140 800 A (GLAXO GROUP LTD.) 5 December 1984 (1984-12-05) cited in the application page 1 -----	1,11



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

1 July 2002

Date of mailing of the international search report

09/07/2002

Name and mailing address of the ISA

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Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/EP 02/02317**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 8 is directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/02317

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2140800	A 05-12-1984	AT 390611 B AT 129184 A AU 573212 B2 AU 2706484 A BE 899448 A1 BE 900835 A4 BG 61490 B2 CA 1335999 A1 CA 1336004 A1 CH 661497 A5 CH 667084 A5 CZ 9104028 A3 CY 1482 A CZ 285602 B6 DE 3414752 A1 DE 3448338 C2 DE 3448452 C2 DK 158092 A DK 201784 A ES 531722 D0 ES 8505641 A1 ES 539625 D0 ES 8609209 A1 FI 841548 A ,B, FR 2545482 A1 GB 2176476 A ,B GR 79925 A1 HK 36889 A HU 200160 B IE 57237 B1 IL 71569 A IT 1199112 B JP 1862136 C JP 5069817 B JP 63264443 A JP 1643826 C JP 3000858 B JP 59199659 A JP 2001385 C JP 6087800 A JP 7029997 B KE 3864 A KR 9204186 B1 LU 85329 A1 LU 88265 A9 MX 9203226 A1 NL 8401258 A ,B, NO 841568 A ,B, NZ 207885 A NZ 221999 A	11-06-1990 15-11-1989 02-06-1988 25-10-1984 18-10-1984 17-04-1985 30-09-1997 20-06-1995 20-06-1995 31-07-1987 15-09-1988 12-05-1993 08-12-1989 15-09-1999 18-10-1984 19-05-1993 05-01-1994 30-12-1992 19-10-1984 01-06-1985 01-10-1985 16-07-1986 16-12-1986 31-12-1986 31-10-1984 12-05-1989 28-04-1990 17-06-1992 30-10-1987 30-12-1988 08-08-1994 01-10-1993 01-11-1988 28-02-1992 09-01-1991 12-11-1984 20-12-1995 29-03-1994 05-04-1995 19-05-1989 30-05-1992 04-06-1985 03-02-1994 01-07-1992 16-11-1984 19-10-1984 29-11-1988 29-11-1988